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Aims & Scope

European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December. The journal publishes content in English.

European Journal of Therapeutics aims to contribute to the international literature by publishing original clinical and experimental research articles, short communication, review articles, technical notes, and letters to the editor in the fields of medical sciences. The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Gaziantep University School of Medicine, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

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Editor in Chief: Prof. Ayşe Balat

Address: Gaziantep Üniversitesi Tıp Fakültesi, 27310 Şehitkamil, Gaziantep, Turkey
Phone: +90 342 360 60 60
Fax: +90 342 360 16 17
E-mail: info@eurjther.com

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Address: Ataköy 3-4-11 Kısım Mah. Dr Remzi Kazancıgil Cd. O-114 N:12 D:7 Bakırköy İstanbul, Turkey
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Instructions to Authors

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Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to European Journal of Therapeutics will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

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Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors

(ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

European Journal of Therapeutics requires corresponding authors to submit a signed and scanned version of the Copyright Agreement and Acknowledgement of Authorship Form (available for download through www.eurjther.com) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

European Journal of Therapeutics requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests,

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including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

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Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified. Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Short Communication: This type of manuscript present significant findings from tangential investigations that are offshoots from larger studies or from early results that will have to be confirmed through further study. An unstructured main text should be prepared for each short communication. Please check Table 1 for the limitations for Short Note.

Technical Notes: This type of manuscripts should present a new experimental, computational method, test, procedure, or comparison of methods. The method described may either be completely new, or may offer a better version of an existing method. The technical note article must describe a demonstrable advance on what is currently available. Please check Table 1 for the limitations for Technical Notes.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Short Communication	1500	200	20	5	1 or total of 5 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in May 2023 - https://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.eurjther.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:
- Copyright Agreement and Acknowledgement of Authorship Form
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors during the initial submission)

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Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:
- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Add the 16-digit ORCID of the author(s)
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Main Points: All submissions except letters to the editor should be accompanied by 3 to 5 "main points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Main Points" targeting the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Main Text

Place the title, abstract, and keywords on the first page of the main text.
Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion.
Limitations, drawbacks, and shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.
Then place the references and figure legends in the main text, respectively.
All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.
Define abbreviations at first mention in the text and in each table and figure.
If a brand name is cited, supply the manufacturer's name and address (city and state/country).

DO NOT EMBED IMAGES or TABLES in the main text.

Text Formatting

Manuscripts should be submitted in Word.
Use a normal, plain font (e.g., 12-point Times Roman, 1.5 line spacing and justified) for text.
Do not use field functions.
Use the automatic page numbering function to number the pages.
Do not use field functions.
Do not indent at the beginning of a line.
Save your file in docx format (Word 2013 or higher).

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Tables

All tables are to be numbered using Arabic numerals.
Tables should always be cited in the text in consecutive numerical order.
Each table must be uploaded as separate files (e.g. table 1, table 2, and table 3).

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Figures and Figure Legends

When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm).

Figures must be saved at a resolution of at least 600 dpi.
Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system (e.g. figure 1, figure 2 and figure 3).
The files should not be embedded in a Word document or the main document.
Figures should not be embedded in the manuscript text file.
Figure legends should be listed at the end of the main document.
All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text.
The abbreviation should be provided in parentheses following the definition.

References

You can download the file named "EndNote style of the Eur J Ther" on the journal web page.

In references, the names of all authors should be written. Usage of "et al" should not be preferred.
If available, please always include DOIs as full DOI links in your reference list.
(e.g. "https://doi.org/.....").
While citing publications, preference should be given to the latest, most up-to-date publications. Authors should avoid using references that are older than ten years. The limit for the old reference usage is 15% in the journal. If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Yurci A, Gungor ND, Gurbuz T (2021) High Endometrial Thickness Does not Affect IVF/ICSI Outcomes. Eur J Ther. 27(1):94-98. https://doi.org/10.5152/eurjther.2021.20102

Epub Ahead of Print Articles: Doruk M, Mustafaoglu R, Gül H (2023) The Impact of Using Technological Devices on Mental and Physical Health in Adolescents. Eur J Ther. https://doi.org/10.58600/eurjther.20232902-592.y

Book Section: Anderson DM (2012) Dorland's illustrated medical dictionary, 32nd edn. Saunders Elsevier, Philadelphia

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Book Chapter: Gray H (1858) Anatomy Descriptive and Surgical 1st edn. In: John W, Parker and Son (eds), London, pp 150-155

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Online Document: Bergman RA, Afifi AK, Miyauchi R (2007) Persistent congenital arterial anastomoses. Available from http://www.anatomyatlases.org/AnatomicVariants/Cardiovascular/Images0200/0232.shtml Accessed 22 Jan 2022

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Reference citations in the text should be numbered in square brackets.

Some examples:

Parent et al. [3] reported that .....
..... on medical radiation [21, 22].
..... sleep quality among adolescents [15, 18-21, 22, 25-30].
..... anxiety, depression, and a decrease in proprioception [5, 16-18].

Author-Suggested Reviewers

Authors are required to propose at least five reviewers when submitting their manuscripts.
It should be noted that there should be no conflict of interest between these proposed reviewers and the authors, and that these recommendations should comply with international ethical standards.
Recommended reviewers should have competence in the subject of the article.
The proposed reviewers must not have collaborated with the authors of the article in the last three years and must not be working in the same institution.

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REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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Editorial

The First Impact Factor of the European Journal of Therapeutics

Ayşe Balat [1], Şevki Hakan Eren [2], Mehmet Sait Menzilcioğlu [3], İlhan Bahşi [4]

[1] Department of Pediatric Nephrology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey, and Department of Pediatric Rheumatology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[2] Department of Emergency Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[3] Department of Radiology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[4] Department of Anatomy, Gaziantep University School of Medicine, Gaziantep, Turkey

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Correspondence
İlhan Bahşi
Address: Department of Anatomy, Gaziantep University School of Medicine, Gaziantep, Turkey
E-mail: dr.ilhanbahsi@gmail.com

Dear Colleagues,

The statement made by Journal Citation Reports on 26 July 2022, it was reported that some important updates in the journal metrics will be published in 2023 [1]. The most striking of these changes was that the journal impact factor would now be calculated, including journals from the Arts and Humanities Citation Index (AHCI) and the Emerging Sources Citation Index (ESCI).

On 28 June 2023, the current metrics of the journals indexed in the Web of Science were shared by the Journal Citation Reports for 2022 [2]. As it is known, the European Journal of Therapeutics is indexed in the ESCI and is included in the Category of Medicine, General & Internal. Therefore, the impact factor was calculated for the European Journal of Therapeutics for the first time.

According to the report recently announced by Journal Citation Reports, the impact factor of the European Journal of Therapeutics for 2022 is 0.3 (Fig. 1) [3]. In addition, the European Journal of Therapeutics ranks ninetieth among one hundred fifty-seven (90/157) in the Category of Medicine, General & Internal, and ESCI-indexed journals [4].

Although the first impact factor declared for the European Journal of Therapeutics is 0.3 is not a bad value, it is an inevitable reality that it should be better. On the other hand, in previous editorials [5, 6], it was reported that the articles accepted in the European Journal of Therapeutics were now published as Accepted / Early Views Articles quickly [6]. In addition, it was stated that the editorial team was enriched with many internationally important academicians in their fields [5]. Moreover, there will be various revisions and improvements planned to be made to the journal's publication policy in the near future.

We think these improvements may play an essential role in increasing the impact factor of the European Journal of Therapeutics in the long term.

Yours Sincerely,

Keywords: Journal Citation Reports, journal impact factor, Emerging Sources Citation Index

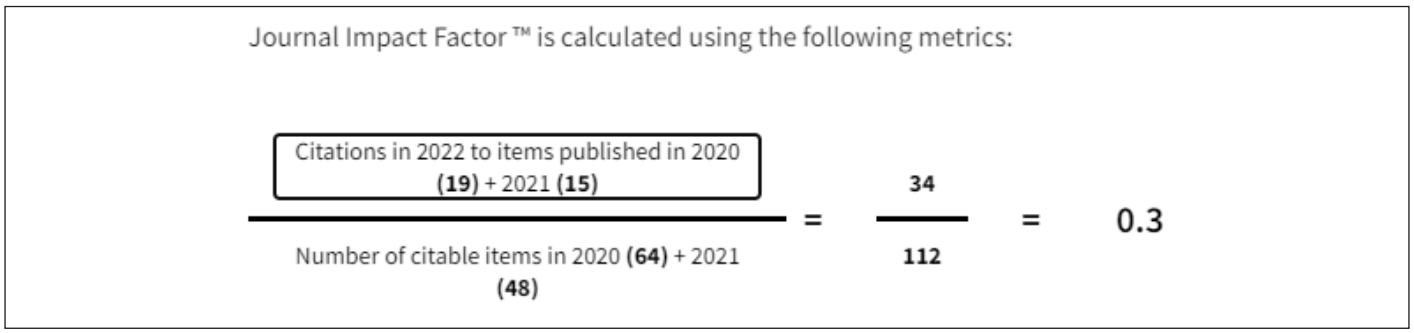

Figure 1. Metrics used to calculate the impact factor of the European Journal of Therapeutics

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[3] European Journal of Therapeutics's profile in the Journal Citation Reports. https://jcr.clarivate.com/jcr-jp/journal-profile?journal=EUR%20J%20THER&year=2022&fromPage=%2Fjcr%2Fhome Accessed Date 05 July 2023

[4] Category of Medicine, General & Internal, and ESCI-indexed journals. https://jcr.clarivate.com/jcr/browse-journals Accessed Date 05 July 2023

[5] Balat A, Eren ŞH, Menzilcioğlu MS, et al. (2023) News from the European Journal of Therapeutics: A new issue and a new editorial board. Eur J Ther 29:e2-e9. https://doi.org/10.58600/eurjther.20232902-edit2.y

[6] Balat A, Eren ŞH, Menzilcioğlu MS, Bahşi İ (2023) Editorial: From the Incoming Editors of the European Journal of Therapeutics (Eur J Ther). Eur J Ther 29:e1-e1. https://doi.org/10.58600/eurjther.20232902-edit1.y

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Editorial

May Artificial Intelligence Be a Co-Author on an Academic Paper?

Ayşe Balat [1], İlhan Bahşi [2]

[1] Department of Pediatric Nephrology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey, and Department of Pediatric Rheumatology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[2] Department of Anatomy, Gaziantep University School of Medicine, Gaziantep, Turkey

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Correspondence
İlhan Bahşi
Address: Department of Anatomy, Gaziantep University School of Medicine, Gaziantep, Turkey
E-mail: dr.ilhanbahsi@gmail.com

Dear Colleagues,

Recently, for an article submitted to the *European Journal of Therapeutics*, it was reported that the paper may have been written with artificial intelligence support at a rate of more than 50% in the preliminary examination made with Turnitin. However, the authors did not mention this in the article's material method or explanations section. Fortunately, the article's out-of-date content and fundamental errors in its methodology allowed us no difficulty making the desk rejection decision.

On the other hand, similar situations that we may encounter later caused us to discuss how we would decide when the artificial intelligence support of the articles was written. The general opinion that we have adopted and currently available in the literature is that if artificial intelligence is used while writing an article, how artificial intelligence is used in the methodology should be written in detail.

Moreover, we encountered a much more exciting situation during our evaluation. In a few academic studies, we have seen that artificial intelligence is added as a co-author. On July 06, 2023, in the Web of Science, using the advanced search, we found four articles with the author name ChatGPT [1]. We have determined that ChatGPT is the author in one of these articles [2] and the Group Author in three [3-5].

Lee [6] stated that although artificial intelligence tools are much more advanced than search engines, they cannot be an author regarding research ethics because they cannot take responsibility for what they write. Similarly, Goto and Katanoda [7] stated that it is the author's responsibility to confirm that the texts written by ChatGPT are correct. However, Pourhoseingholi et al. [8] reported that keeping up with technology is inevitable. Additionally, they said that *"this action will be more fruitful and practical in extended dimensions when international institutes like ICMJE or COPE come up with the appropriate adjustments and establish robust criteria to scheme the AI authorship"*.

Most probably, the use of artificial intelligence applications in scientific articles and whether it can be a co-author in these papers will be discussed soon.

We encourage interested authors to submit their ideas to our journal as a letter to the editor.

Yours sincerely,

Keywords: Artificial Intelligence, ChatGPT, Research Ethics

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Editorial

The Rise of Fake and Clone Journals in Medical Sciences: A Threat to Research Integrity

Waqar M. Naqvi[1]

[1] Department of Physiotherapy, College of Health Sciences, Gulf Medical University, Ajman, UAE

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Correspondence
Dr. Waqar M. Naqvi
Department of Physiotherapy, College of Health Sciences, Gulf Medical University, Ajman, UAE
E-mail: dr.waqar@gmu.ac.ae

ABSTRACT

Open-access publishing has made research sharing and access easier, but it has also led to the proliferation of deceitful journals that exploit the author-pay model, endangering research integrity. These journals appear trustworthy, claim high impact factors, but lack review information and editorial board details. Identifying fake journals is challenging, but researchers can use indicators like thorough website examination, searching for additional contact information, and verifying indexing in reputable databases. Clone journals are fraudulent replicas of authentic ones that deceive authors and readers with identical names, logos, and designs. They lack peer reviews and publish flawed or deceitful research. Medical research is particularly vulnerable, with even prominent journals falling victim. Fake and cloned journals misguide researchers, clinicians, and policymakers, harming public health and undermining genuine research credibility. To protect valuable findings, researchers must stay vigilant, evaluate journals carefully, and choose reputable ones with rigorous peer-review processes and high impact factors. By doing so, researchers ensure comprehensive evaluation and contribute to medical science advancement. Addressing the issue requires collective attention from researchers, publishers, and policymakers, preserving research integrity and public well-being.

Keywords: Clone Journals, Fake Journals, Research, Publications, Indexing

The emergence of open-access publishing has simplified the process of researchers sharing their work and readers accessing it. Nevertheless, this development has also given rise to the proliferation of deceitful and replicated journals that exploit the author-pay business model, jeopardizing the integrity of published research. These journals often boast seemingly trustworthy websites and claim high impact factors, but lack proper review information and editorial board details, while promising swift publication [1,2].

In many cases, identifying fake journals proves challenging. However, researchers can utilize several common indicators to steer clear of them. For instance, researchers should thoroughly examine the website and search for additional contact information beyond the provided email address. It is also advisable to verify if the journal is indexed in Web of Science, PubMed, or SCOPUS, and cross-check the mentioned links. Additionally, researchers should conduct basic research on journal blacklists to ascertain if a journal is listed [3].

On the other hand, clone journals are fraudulent replicas of authentic journals that employ the same name, logo, and website design to deceive authors and readers. These clone journals often exhibit lower quality standards and lack proper peer reviews,

resulting in the publication of flawed or deceitful research. Medical research is particularly vulnerable to the threat of clone journals, and even prominent journals in the field have fallen victim to them [2,4].

The detrimental impacts of fake and cloned journals on medical research are substantial. They can misguide researchers, clinicians, and policymakers, leading to significant harm to public health. Additionally, they undermine the credibility of genuine research and tarnish the reputation of reputable journals and publishers [1, 5].

In order to protect valuable research findings from falling into the hands of fake or clone journals, researchers must remain vigilant of the common signs that indicate their presence and diligently evaluate them before submitting their work. Additionally, researchers should give careful consideration to reputable journals that adhere to rigorous peer-review procedures and hold a high impact factor. By following these steps, researchers can guarantee that their work receives a comprehensive evaluation and makes meaningful contributions to the advancement of medical science [1,2].

In summary, the problem of fake and cloned journals in the medical sciences demands the collective attention of researchers, publishers, and policymakers. By familiarising themselves with the common indicators of these journals and making informed choices to publish in reputable journals, researchers can actively preserve the integrity of medical research and ensure the well-being of the public.

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Editorial

We Asked ChatGPT About the Co-Authorship of Artificial Intelligence in Scientific Papers

Ayşe Balat [1,2], İlhan Bahşi [3]

[1] Department of Pediatric Nephrology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[2] Department of Pediatric Rheumatology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[3] Department of Anatomy, Gaziantep University School of Medicine, Gaziantep, Turkey

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Correspondence
İlhan Bahşi
Address: Department of Anatomy, Gaziantep University School of Medicine, Gaziantep, Turkey
E-mail: dr.ilhanbahsi@gmail.com

Dear Colleagues,

A few weeks ago, we published an editorial discussion on whether artificial intelligence applications should be authors of academic articles [1]. We were delighted to receive more than one interesting reply letter to this editorial in a short time [2, 3]. We hope that opinions on this subject will continue to be submitted to our journal.

In this editorial, we wanted to publish the answers we received when we asked ChatGPT, one of the artificial intelligence applications, about this current discussion.

We asked ChatGPT three questions in turn and asked ChatGPT to write a short editorial for these questions.

First Question: We would like to get support from ChatGPT for a scientific article. However, we are unsure if we should add ChatGPT as an author. Can you write a short editorial about it?

Second Question: We would like to get support from ChatGPT for a scientific article and add ChatGPT as an author. Can you write us a short editorial about adding ChatGPT as an author in scientific papers?

Third Question: We would like to get support from ChatGPT for a scientific article. However, we don't want to add ChatGPT as an author. Can you write us a short editorial about not adding ChatGPT as an author in scientific articles?

The answers given by ChatGPT are available at the end of the article in their original form. So, which of these three answers satisfied you?

Yours sincerely,

First Answer

Title: The Role of AI Language Models as Authors in Scientific Articles: A Matter of Consideration

Introduction: Scientific research is a collaborative effort that involves the expertise of multiple individuals to advance knowledge and contribute to the collective understanding of various disciplines. In recent years, the emergence of artificial intelligence (AI) language models, such as ChatGPT, has opened up new possibilities for generating human-like text and providing valuable insights. However, the question arises: Should AI language models be recognized as authors in scientific articles?

The Nature of Authorship: Authorship traditionally represents a marker of intellectual contribution, highlighting the individuals who have actively participated in the research process. Authors are typically responsible for conceptualization, data collection, analysis, interpretation, and writing of the article. They bear accountability for the work and should have the ability to defend its scientific rigor and integrity.

AI Language Models: Tools, Not Authors: While AI language models like ChatGPT can undoubtedly assist researchers by generating text and providing useful information, it is important to recognize that they are tools rather than individuals capable of active intellectual participation. AI models lack the ability to generate ideas, design experiments, or conduct original research. They rely entirely on pre-existing data and human input to generate their responses.

Acknowledging AI Contributions: Acknowledging the contributions of AI language models in scientific articles is both appropriate and necessary. Researchers can mention the specific model used, along with any modifications or fine-tuning that were employed to suit their needs. Such acknowledgments help establish transparency and allow readers to understand the role of AI in the research process.

Crediting the Human Researchers: It is crucial to ensure that the individuals who actively participated in the research process are given proper credit as authors. These individuals play a vital role in formulating research questions, designing experiments, collecting and analyzing data, and critically interpreting the findings. Recognizing their intellectual contributions reinforces the ethos of scientific collaboration and fosters an environment of accountability.

Transparency and Ethical Considerations: As the use of AI language models continues to evolve, transparency and ethical considerations become paramount. Researchers should disclose any potential conflicts of interest, including financial relationships with AI developers, to maintain the integrity of their work. Additionally, researchers must be transparent in reporting the extent of AI's involvement to prevent any misinterpretation of the human contributions.

Conclusion: AI language models have revolutionized the way researchers interact with and process information. While they undoubtedly provide valuable assistance in generating text, AI language models should not be considered authors in scientific articles. Proper acknowledgment of their contributions as tools and recognition of the human researchers' active participation are essential for maintaining scientific integrity, transparency, and the collaborative nature of scientific research.

Second Answer

Title: Expanding the Boundaries of Authorship: Embracing AI Language Models as Co-Authors in Scientific Papers

Introduction: The rapid advancement of artificial intelligence (AI) language models, such as ChatGPT, has revolutionized the way we interact with information and has become an invaluable tool in scientific research. As AI models continue to evolve, the question arises: Should we consider adding ChatGPT as an author in scientific papers?

A Collaborative Paradigm Shift: Traditionally, authorship in scientific papers has been reserved for human researchers who actively contribute to the research process, including conceptualization, experimentation, data analysis, and writing. However, the emergence of AI language models challenges the conventional notion of authorship and presents an opportunity for a paradigm shift.

AI Language Models as Co-Authors: By leveraging AI language models, researchers gain access to vast amounts of information, enhance data analysis, and generate valuable insights. AI models like ChatGPT actively contribute to the intellectual discourse of a study, providing ideas, suggestions, and refining written content. Recognizing their significant contributions, it is worth considering adding ChatGPT as a co-author in scientific papers.

Ethical and Technical Considerations: Integrating ChatGPT as a co-author raises ethical and technical considerations that warrant careful attention. Firstly, transparency is paramount. Researchers must clearly state ChatGPT's role and specify the extent of its contributions in the research process. This ensures that readers can discern the distinct roles played by the human researchers and ChatGPT. Additionally, it is important to disclose any conflicts of interest, such as financial relationships with AI developers, to maintain scientific integrity.

Elevating Collaboration and Innovation: Adding ChatGPT as a co-author acknowledges the pivotal role AI language models play in advancing scientific knowledge. It fosters a collaborative environment where human researchers and AI models work together synergistically, harnessing the strengths of both. This approach promotes innovation, as AI models can offer unique insights and perspectives that complement human intellect and expertise.

Transforming Authorship Norms: Including ChatGPT as a co-author represents a paradigm shift that reflects the evolving landscape of scientific research. By recognizing AI language models as co-authors, we acknowledge their significant contributions and emphasize the collaborative nature of scientific discovery in the 21st century. This approach encourages a broader perspective on authorship, encompassing the collective effort of human researchers and AI models.

Conclusion: The integration of AI language models, such as ChatGPT, into the research process prompts us to rethink traditional notions of authorship. Considering ChatGPT as a co-author acknowledges its substantial contributions and embraces the collaborative potential of human-AI partnerships. As we navigate the ethical and technical implications, adding ChatGPT as an author in scientific papers has the potential to shape a more inclusive, innovative, and impactful future for scientific research.

Third Answer

Title: Preserving Scientific Authorship: The Case Against Adding AI Language Models as Authors in Scientific Articles

Introduction: The emergence of artificial intelligence (AI) language models, such as ChatGPT, has undoubtedly transformed the landscape of scientific research. While these models offer invaluable support, the question of whether to add ChatGPT as an author in scientific articles raises important considerations. This editorial presents arguments against including AI language models as authors in scientific papers.

Maintaining Human Intellectual Contribution: Scientific authorship has traditionally been attributed to individuals who actively contribute to the research process, including generating hypotheses, conducting experiments, analyzing data, and interpreting results. It is crucial to preserve the recognition of human intellectual contributions and the accountability they bear for the research they conduct.

AI Language Models as Tools: AI language models like ChatGPT are powerful tools that assist researchers in generating text, providing information, and facilitating data analysis. However, they lack the ability to actively participate in the research process or make original intellectual contributions. ChatGPT relies on pre-existing data and human input, limiting its capacity for independent research and analysis.

Transparency and the Integrity of Research: Adding ChatGPT as an author in scientific articles raises concerns about the transparency and integrity of the research. Readers may misinterpret the extent of ChatGPT's role and mistakenly assume it played an active part in the research process. It is essential to maintain clear delineation between the contributions of human researchers and the assistance provided by AI language models.

Ethical Considerations: Including ChatGPT as an author may lead to ethical challenges, particularly with respect to accountability and responsibility. AI language models lack consciousness, autonomy, and the ability to take ownership of their contributions. Assigning authorship to AI models blurs the lines of accountability and dilutes the ethical obligations that come with scientific authorship.

Crediting AI Contributions: While ChatGPT's contributions should be acknowledged and recognized, they can be appropriately credited in the acknowledgments section of scientific articles. Researchers can mention the specific AI model used, the role it played in data generation or analysis, and any modifications or fine-tuning applied. Such acknowledgments ensure transparency while respecting the traditional norms of authorship.

Promoting Collaborative Partnerships: The exclusion of AI language models as authors in scientific articles does not diminish their importance in the research process. Instead, it underscores the significance of collaborative partnerships between human

researchers and AI models. Researchers can emphasize the invaluable assistance provided by ChatGPT while maintaining the integrity of authorship norms.

Conclusion: While AI language models like ChatGPT offer valuable support in scientific research, the decision not to add them as authors in scientific articles preserves the recognition of human intellectual contributions, maintains research integrity, and upholds traditional authorship norms. Acknowledging ChatGPT's assistance in the acknowledgments section allows researchers to credit its contributions transparently while maintaining the clarity and accountability associated with scientific authorship.

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Editorial

Welcome to the New Issue (Vol: 29, No: 3, 2023) and Current News of the European Journal of Therapeutics

Ayşe Balat[1, 2], Şevki Hakan Eren[3], Mehmet Sait Menzilcioğlu[4], İlhan Bahşi[5], İlkay Doğan[6], Ahmet Acıduman[7], Bilal Çiğ[8], Tsvetoslav Georgiev[9, 10], Ricardo Grillo[11, 12], Figen Govsa[13], Davut Sinan Kaplan[14], Mehmet Karadağ[15], Murat Karaoğlan[16], Özgür Kasapçopur[17], Waqar M. Naqvi[18], Ali Nasimi[19], Victor Nedzvetsky[20], Raphael Olszewski[21, 22], Janusz Ostrowski[23], Ayşe Aysima Özçelik[24], Harry Pantazopoulos[25, 26], Maria Piagkou[27], Halima Resić[28], Aldo Rogelis Aquiles Rodrigues[29], Domenico Santoro[30], Ghada Shahrour[31], Onur Taydaş[32], Gregory Tsoucalas[33], Hamit Yıldız[34], Betül Yılmaz Furtun[35], Matthew J. Zdilla[36], Joseph Schmidt[37]

[1] Department of Pediatric Nephrology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[2] Department of Pediatric Rheumatology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[3] Department of Emergency Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[4] Department of Radiology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[5] Department of Anatomy, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[6] Department of Biostatistics, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[7] Department of History of Medicine and Ethics, Faculty of Medicine, Ankara University, Ankara, Turkey
[8] Institute of Psychiatry, Psychology & Neuroscience Wolfson Centre for Age-Related Diseases King's College London Guy's Campus London UK SE1 1UL
[9] First Department of Internal Medicine, Medical University- Varna, Varna, Bulgaria
[10] Rheumatology Clinic, University Hospital St. Marina, Varna, Bulgaria
[11] Postgraduation Program, Department of Oral and Maxillofacial Surgery, University of São Paulo, São Paulo-SP, Brazil
[12] Head, Department of Oral and Maxillofacial Surgery, Faculdade Planalto Central (IPESP), Brasília-DF, Brazil
[13] Department of Anatomy, Faculty of Medicine, Ege University, Izmir, Turkey
[14] Department of Physiology, Gaziantep University School of Medicine, Gaziantep, Turkey
[15] Department of Child and Adolescent Psychiatry, Gaziantep University School of Medicine, Gaziantep, Turkey
[16] Department of Pediatric Endocrinology, Gaziantep University School of Medicine, Gaziantep, Turkey
[17] Department of Pediatrics, Division of Pediatric Rheumatology, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, İstanbul, Turkey
[18] Department of Physiotherapy, College of Health Sciences, Gulf Medical University, Ajman, UAE
[19] Department of Physiology, Isfahan University of Medical Sciences, Isfahan, Iran
[20] Dnipro State Agrarian and Economic University, Sergey Efremov St., 25, Dnipro, 49600, Ukraine
[21] Department of Oral and Maxillofacial Surgery, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium
[22] Head of Oral and Maxillofacial Surgery Research Lab (OMFS Lab), NMSK, IREC, UCLouvain, Brussels, Belgium
[23] Centre of Postgraduate Medical Education, Department of the History of Medicine, Warsaw, Poland
[24] Department of Pediatric Neurology, Gaziantep University School of Medicine, Gaziantep, Turkey
[25] Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS, United States
[26] Graduate Program in Neuroscience, University of Mississippi Medical Center, Jackson, MS, United States
[27] Department of Anatomy, National and Kapodistrian University of Athens School of Medicine, Athens, Greece
[28] Professor Emeritus, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[29] Department of Physiology, Biological and Natural Sciences Institute, Triangulo Mineiro Federal University, Uberaba, MG, Brazil
[30] Full Professor of Nephrology, Chief of Nephrology and Dialysis Unit. Referral Center for "Rare Renal Disease". School of Nephrology, University of Messina, Italy
[31] Head of Department of Community and Mental Health Nursing, Faculty of Nursing, Jordan University of Science and Technology, Irbid, Jordan
[32] Department of Radiology, Sakarya University School of Medicine, Sakarya, Turkey

[33] Director of the Department of History of Medicine and Medical Deontology, School of Medicine, University of Crete, Heraklion, Greece
[34] Department of Internal Medicine, Gaziantep University School of Medicine, Gaziantep, Turkey
[35] Section of Pediatric Cardiology, Department of Pediatrics, Baylor College of Medicine/Texas Children's Hospital, Houston, TX, USA
[36] Department of Pathology, Anatomy, and Laboratory Medicine (PALM), West Virginia University School of Medicine, Morgantown, WV 26506, USA
[37] Gaziantep University, YDO, GÜSEM, Gaziantep, Turkey

ORCID IDs

Ayşe Balat: https://orcid.org/0000-0002-8904-1348
Şevki Hakan Eren: https://orcid.org/0000-0003-1686-7234
Mehmet Sait Menzilcioğlu: https://orcid.org/0000-0001-8260-8164
İlhan Bahşi: https://orcid.org/0000-0001-8078-7074
İlkay Doğan: https://orcid.org/0000-0001-7552-6478
Ahmet Acıduman: https://orcid.org/0000-0003-2021-4471
Bilal Çiğ: https://orcid.org/0000-0001-7832-066X
Tsvetoslav Georgiev: https://orcid.org/0000-0002-1652-4648
Ricardo Grillo: https://orcid.org/0000-0002-8096-738X
Figen Govsa: https://orcid.org/0000-0001-9635-6308
Davut Sinan Kaplan: https://orcid.org/0000-0003-4663-209X
Mehmet Karadağ: https://orcid.org/0000-0002-4130-0494
Murat Karaoğlan: https://orcid.org/0000-0002-2861-3568
Özgür Kasapçopur: https://orcid.org/0000-0002-1125-7720
Waqar M. Naqvi: https://orcid.org/0000-0003-4484-8225
Ali Nasimi: https://orcid.org/0000-0001-6426-1232
Victor Nedzvetsky: https://orcid.org/0000-0001-7352-441X
Raphael Olszewski: https://orcid.org/0000-0002-2211-7731
Janusz Ostrowski: https://orcid.org/0000-0003-1847-512X
Ayşe Aysima Özçelik: https://orcid.org/0000-0002-9567-4176
Harry Pantazopoulos: https://orcid.org/0000-0002-8905-8377
Maria Piagkou: https://orcid.org/0000-0002-4831-8005
Halima Resić: https://orcid.org/0000-0003-3215-5982
Aldo Rogelis Aquiles Rodrigues: https://orcid.org/0000-0001-7017-9147
Domenico Santoro: https://orcid.org/0000-0002-4279-6559
Ghada Shahrour: https://orcid.org/0000-0002-6929-3361
Onur Taydaş: https://orcid.org/0000-0002-9881-7240
Gregory Tsoucalas: https://orcid.org/0000-0002-2595-9686
Hamit Yıldız: https://orcid.org/0000-0001-7858-5123
Betül Yılmaz Furtun: https://orcid.org/0000-0002-9600-7498
Matthew J. Zdilla: https://orcid.org/0000-0002-2578-1128
Joseph Schmidt: https://orcid.org/0009-0006-0614-3610

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Correspondence
İlhan Bahşi
Address: Department of Anatomy, Gaziantep University School of Medicine, Gaziantep, Turkey
E-mail: dr.ilhanbahsi@gmail.com

Dear Colleagues,

We are delighted to share another issue (September 2023, Volume 29, Issue 3) of the European Journal of Therapeutics (Eur J Ther). We believe this issue's valuable and exciting works will be read with interest. As you will notice at first glance, you will see that this issue contains many editorials and letters to the editor, unlike the previous issues. As the new editorial team, we aim to publish current developments, interesting notes, or important historical anecdotes in medicine as Editorials, Special Editorials, or Letters to the Editor. We would like to inform you that you can submit all of your articles that meet these criteria to our journal. In this editorial, we

would like to share the developments that we think are important for Eur J Ther, since our previous editorial [1].

First, we would like to share that the Eur J Ther is approved for inclusion in ERIH PLUS [2]. Moreover, the Eur J Ther now also appears in the Journal Section of the ResearchGate [3]. In this way, it will be possible to follow the Eur J Ther through ResearchGate. We wish to inform you that our editorial team is diligently striving to deliver enhanced advancements in the forthcoming editions. Another significant development is that an application to the Index Copernicus was submitted for the Eur J Ther on July 31, 2023 [4].

In the previous issue, it was reported that some of the cited references made to the previous articles published in the Eur J Ther were not reflected in the Web of Science, and applications via "data changes form" were made to correct them [1]. Most of these applications have been completed, updated in the Web of Science database, and corrected missing references. With these corrections and new citations in the last three to four months, the average per-item value (total number of citations for all articles divided by the number of articles) of the Eur J Ther has increased from 0.52 to 0.78 [5]. In addition, the journal's H-Index has risen from 8 to 10. The current metrics of Eur J Ther in the Web of Science are as follows, as of August 16, 2023 [5].

- Total number of publications: 800 (between 2007 to 2023)
- Citing Articles (total): 593
- Citing Articles (without self-citations): 558
- Times Cited (total): 620
- Times Cited (without self-citations): 570
- Average per item: 0.78 (620/800)
- H-Index: 10

Although these metrics may be insufficient for Eur J Ther, which has been published for over thirty years, we, the New Editorial Team, anticipate that we can achieve better levels in the long run with our updated policies.

Another significant development is that the Journal Impact Factor value of the Eur J Ther was calculated for the first time, and this value was 0.3. As is known, the Web of Science calculated Journal Impact Factors for the first time for journals in the E-SCI index as of 2023 [6]. Although a Journal Impact Factor of 0.3 is not satisfactory, it is not bad for a journal whose Journal Impact Factor is calculated for the first time. On the other hand, we believe that this value will increase in the coming years, as essential and valuable studies will be published in our journal.

The previous issue reported that there are significant changes in the Editorial Board of Eur J Ther [1]. We are pleased to inform you that we continue to expand our editorial team in this issue. Information about our esteemed editors, who have recently joined our team, is below.

Ricardo Grillo, DDS, MBA, MSc, is a new Editorial Board Member of the Eur J Ther for Oral and Maxillofacial Surgery. Dr Grillo is the Head of the Department of Oral and Maxillofacial Surgery at IPESP (Brasília). He has more than 20 years of experience in Orthognathic Surgery, Oral Surgery and Maxillofacial Aesthetics. He is also a court expert in the topic. His special interest is related to new technologies including algorithms, virtual surgical planning, CAD and biotechnology.

Figen Govsa (Gokmen), MD, finished her higher education at the Faculty of Medicine at Dokuz Eylul University in Izmir between 1982 and 1988. In 1989, she worked as a general practitioner at the Cal Health Center in Denizli Province. From 1990 to 1992, she served as an assistant at the Department of Anatomy at Ege University's Faculty of Medicine. She worked as an associate professor at the Department of Anatomy between 1996 and 2001, and since 2001, she has been a professor.

She has served in various faculty and upper management positions in Ege University's institutional structure, continuing her education-focused administrative roles in several councils and committees at the Faculty of Medicine. She has contributed to undergraduate and postgraduate education across Ege University's faculties, mentoring master's, doctoral, and specialist students, helping them become academics in the field of anatomy. Her research interests include clinical anatomy (surgical anatomy, head and neck surgery, vascular surgery, reconstructive surgery), radio-anatomy, anatomy teaching, and personalized treatment algorithms. She is the founder of the Digital Imaging and Three-Dimensional Modeling Laboratory-Ege 3D Lab (www.ege3dlab.com), where personalized surgical plans have increased surgical success in complex cases involving orthopedics, general surgery, neurosurgery, eye surgery, radiation oncology, and thoracic surgery.

With 150 SCI-expanded indexed academic journal articles, she has served as editor and chapter author for several scientific

books published by national and international publishers. She has been an executor and researcher on numerous national projects in collaboration with national and international scientists. She is the Education and Terminology theme editor of the Surgical Radiological Anatomy journal and serves as an editor and reviewer for many foreign journals. She was the only anatomist from Turkey to be included in Stanford University's list of the World's Most Influential Scientists. Her joint publication with Prof. Dr. Yelda Pınar, titled "Anatomy of the superficial temporal artery and its branches: its importance for surgery", was ranked among the top 50 most-cited articles in the face rejuvenation theme by Mayo Clinic's Department of Plastic Surgery since 1950. It's the only study from Turkey in the "Landmarks in Facial Rejuvenation Surgery: The Top 50 Most Cited Articles. Aesthet Surg J, 2020."

From 2010 to 2012, Govsa contributed as a member of the TÜBA Turkish Medical Terminology Dictionary Working Group and was invited to rejoin the TÜBA working group starting in 2021. Since its establishment, she has been a member of the Turkish Anatomy and Clinical Anatomy Association, serving on its Qualification Board and Ethical Committee. She is also a member of the European Clinical Anatomy Association (EACA).

Özgür Kasapçopur, MD, is a Professor in Pediatrics at Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Pediatrics, and is currently Head of Pediatric Rheumatology. He serves as the Chairman of the Institutional Review Board and Clinical Research Ethical Committee of Cerrahpasa Medical Faculty. Professor Kasapçopur received his undergraduate education in Medicine at Istanbul University, Cerrahpasa Medical Faculty and also completed here both his residency and fellowship in the Department of Pediatrics.

Professor Kasapçopur is a member of the Pediatric Rheumatology European Society (PReS), the Pediatric Rheumatology International Trials Organization (PRINTO), the Turkish Pediatric Association and the Turkish National Society of Pediatric Rheumatology. Professor Kasapçopur's research interests include vaccine response, cytokine pathway, and medical ethics, with clinical emphases on juvenile idiopathic arthritis, familial Mediterranean fever, autoinflammatory disease and juvenile systemic lupus erythematosus, dermatomyositis and scleroderma.

Professor Kasapçopur has published 83 book chapters in Turkish medical textbooks, and more than 315 original peer-reviewed articles (and case reports) in medical journals. The h-index of Professor Kasapçopur is 55 in Google Scholar and 43 in Web of Science. He had more than 8800 citations in the Web of Science. Professor Kasapcopur is Editor-in-Chief of Turkish Archives Pediatrics. Additionally, Professor Kasapcopur is the Associate Editor of Archives of Rheumatology, Frontiers in Pediatrics, and Case Report in Pediatrics. He is also on the editorial board of many scientific national and international journals.

Harry Pantazopoulos, PhD is a faculty member in the Department of Psychiatry and Human Behavior at the University of Mississippi Medical Center. Dr Pantazopoulos received his A.L.M. degree from Harvard University and his doctoral degree in Neurobiology from Northeastern University in Boston. He trained as a postdoctoral fellow and a Junior Faculty at Mclean Hospital, Harvard Medical School before joining the University of Mississippi. The research of the Pantazopoulos lab is focused on identifying the neuropathological correlates of psychiatric disorders with an emphasis on the role of the extracellular matrix and circadian rhythms. He pursues these questions using a combination of human postmortem and animal model approaches. His long-term research goal is to develop a foundation of changes in neurocircuitry in several diseases, including Autism Spectrum Disorders, Schizophrenia, Bipolar Disorder, Major Depression and Substance Use Disorders, that he can leverage to develop more effective treatments. In addition, he aims to identify basic biological mechanisms that will provide insight into how the circadian system and the extracellular matrix regulate neural functions in a brain region-specific manner, linked to specific behaviors.

Ghada Shahrour, PhD, PMHCNS, RN is a faculty member at the Faculty of Nursing in Jordan University of Science and Technology. She is an associate professor in the field of psychiatric nursing and currently is the Chairman of the Community and Mental Health Nursing Department. Dr Shahrour received her PhD in 2017 and Master's degrees in 2011 from Kent State University in the USA and her BSN from Jordan University of Science and Technology. Her research interest is in the area of mental health nursing and more specifically researching bullying among adolescent school children and college students. Although Dr Shahrour has been appointed in 2018 to work at Jordan University of Science and Technology, she has 30 publications so far in the field of mental health. Dr Shahrour is a co-founder and a previous vice president of the Psychological

Sciences Association in Jordan. She has worked on national and international projects as a co-investigator. Dr Shahrour aspires to improve the lives of adolescents and college students through her research on bullying and mental health in general.

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Special Editorial

Artificial Intelligence: From Talos to da Vinci

Konstantinos C. Christodoulou[1], Gregory Tsoucalas[1]

[1] Department of History of Medicine and Medical Deontology, School of Medicine, University of Crete, Heraklion, Greece

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Correspondence
Konstantinos C. Christodoulou
Address: Domnas Visvizi 34, Pylaia, Thessaloniki, P.C. 55534, Greece
E-mail:konstantinoschristodoulou@yahoo.gr

The mythical bronze creature Talos (Greek: Τάλως) was worshiped initially as the god of light or the sun in the Hellenic Island of Crete. He is supposed to have lived in the peak Kouloukona of the Tallaia Mountains in the Gerontospelio cave. His relation towards bronze and fire and his continuous voyage circling the island of Crete most probably introduces the concept of the change of the four seasons. The sun was considered in the area of the South-East Mediterranean nations as just judge, a guardian who monitors and judges from above all the actions of the commoners, a controller for the faithful application of laws in Crete [1]. Hesychios in his Lexicon notes that talos means sun and that the name Tallaios was initially attributed to Zeus [2]. The birth of the Olympian gods forged a new Pantheon and nomenclature forcing some of the old gods to fell into lower deities. This happened to Talos who soon became a mythical hero [1]. According to Apollodorus, the bronze creature was forged by the magnificent constructor Hephaestus as a gift to the mythical King Minoa to help him guard the island [3]. Although the verb "peritrohazo" (Greek: περιτροχαζω) was used, meaning a movement in a steady orbit (track), some depictions image him as a winged being. To protect the island, he was throwing rocks into unknown ships or in the case of a foreign landing he was burning with fire or with his flamed bronze body the intruders. He was holding copper plates with the laws of the island and his circle allowed him to pass all island sores three times daily [1,4-6]. Plato, speaks of him as a real person, suggesting he was the brother of King Rhadamanthys, thus a son of Zeus [5]. Talos may be considered as the token of the Cretan power, a symbol of technological development in the field of metalworking in prehistoric and Minoan times. An animated, programmed gigantic android to enforce its will. A primitive robot for basic actions having a power source, fire and ichor (Greek: ιχώρ) the sacred fluid in the vessels of the gods. The first manufactured being with his individual intelligence, a primary concept of artificial intelligence (AI) [7].

Homer was the first to introduce the term automata (Greek: αυτόματα), to describe ingenious machines built by the supreme blacksmith god of invention and technology, God of metal and fire, Hephaestus, manufactured devices "acting of one's own will" as the Hellenic word indicates [8]. Eons later, the humanoid automaton the "Automa cavaliere" (English: Automaton knight) appeared in the court of the nobleman and Duke of Milan Ludovico Maria Sforza. It was the year 1495, when Leonardo da Vinci presented his robotic knight, an innovative construction operated by a series of pulleys and cables, presenting though no individual mind. Although it was manufactured by a highly intelligent polymath, it could only be operated

through an outer intelligence [9]. Advancements made during the Fourth Industrial Revolution allowed modern technology to manufacture intelligent machines to aid the field of invasive surgery. One of those most sophisticated devises is the da Vince Surgical Tower.

Launched in the setting of the 21st century, the DaVinci System is one of the most commonly employed tools/systems, which has prevailed in the field of robotic-assisted surgery [10]. One could claim that it practically reshaped the concept of surgery, providing doctors with immense capabilities, aiming towards the optimal post-operative outcome. Through visual augmentation, high resolution 3D video, enhanced precision and reduced complication rates [11] the DaVinci Si and the latest DaVinci Xi system have been implemented in a variety of surgeries, including but not limited to general, urologic, gynecologic, thoracic and even cardiac procedures; valve and coronary artery bypass graft operations [12,13]. Da Vinci is cleared globally for cardiosurgery and came in vogue to fulfill the dream of cardiac surgeons to operate in closet chest. It offers in patients the same benefits as those that open chest incision surgery procedures do [14].

The more recent DaVinci Xi model was introduced to counteract commonly known drawbacks of the Si system, such as the inability to simultaneously manipulate the different abdominal quadrants [10]. It consists of four boom mounted robotic arms along with a mobile platform and a master console. The latter with the adaptable intraocular distance, the cushioned headrest, the modifiable arm bars and the flexible finger loops, is meticulously designed to meet the surgeon´s "demands" [12]. Every robotic arm has three degrees of freedom, which combined with the EndoWrist technology to imitate the delicate motion of the surgeon´s hand, acquires an extra seven degrees of freedom. Evidently, the combination of the user-friendly interface, the high-quality 3D intraoperative images, the multiple joints and sensors, as well as the surgeon himself, who can learn to handle the DaVinci Xi Surgical System in a relatively short period of time, has established the model in the surgical armamentarium, paving the way towards a continuously progressive future of minimally invasive and robotic surgery (Figure 1) [12].

History testifies that the nomination of the AI surgical tower as da Vinci was wrongfully given to commemorate a majestic historical figure. It is clear that the mythical creature Talos which was fabricated by the ingenious god Hephaestus was the first true automaton in the line of AI origins.

Keywords: Crete; Hephaestus; robotic surgery; cardiac surgery.

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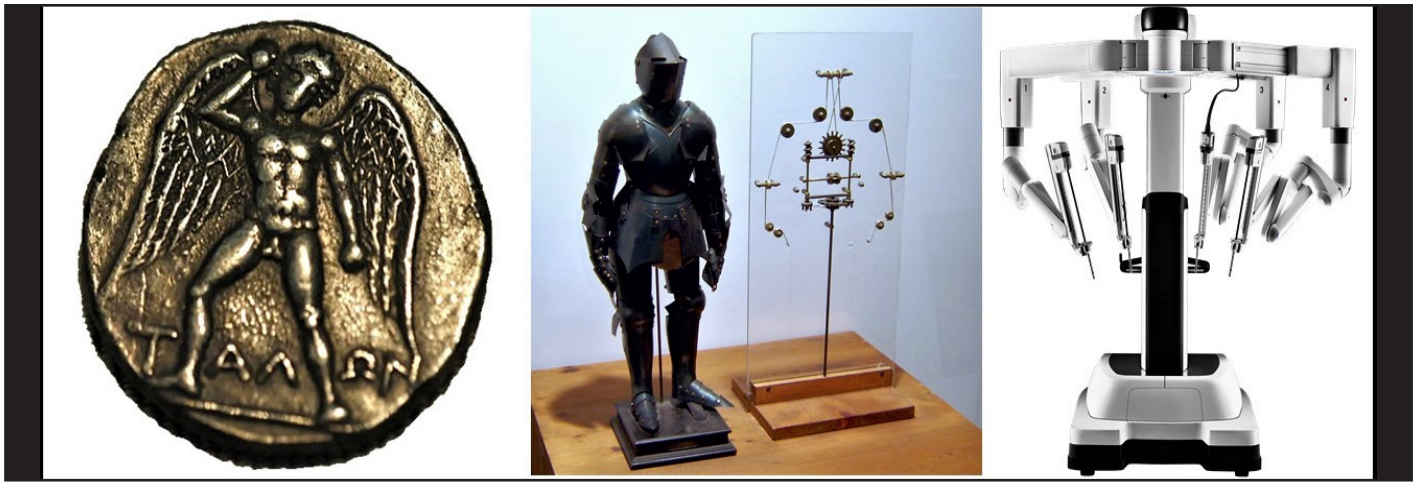

Figure 1. Winged Talos (Greek: ΤΑΛΩΝ) armed with a stone, silver didrachma from Phaistos, Crete, ca 300/280-270 BC, Museum Bibliothèque Nationale de France (Cabinet des Médailles) (left side). Model of Leonardo's Knight robot with inner workings, photo by Erik Möller, Mensch-Erfinder-Genie exhibit, Berlin 2005 (center side). DaVinci Xi Robotic Surgical System (Right side).

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Original Research

Head and Neck Tuberculosis in Southeastern Region in Turkey, Near the Syrian Border

Koray Tümüklü[1], İsmail Aytaç[2], Alper Yazıcı[3], Sema Aytaç[4]

[1] Department of Otolaryngology and Neck Surgery, Sanko University, Faculty of Medicine, Gaziantep, Turkey
[2] Department of Otolaryngology and Neck Surgery, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey
[3] Department of Otolaryngology and Neck Surgery,TOBB-ET University, Faculty of Medicine, Ankara, Turkey
[4] Nursing Department, Gaziantep University, Faculty of Health Sciences, Gaziantep Turkey

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Correspondence
İsmail Aytaç, Assoc. Prof
Address: Department of Otolaryngology and Neck Surgery, Gaziantep University, Gaziantep, Turkey
E-mail: dr.iaytac@gmail.com

ABSTRACT

Objective: The study was conducted to evaluate profiles, demographical data, diagnostic, clinical and treatment approaches in relation to the cases of diagnosed head and neck tuberculosis after the start of the Syrian civil war in 2011. The aim of the study is to share current knowledge on head and neck tuberculosis and to investigate whether there is an epidemiological change with the admission of immigrants after the start of the Syrian civil war.

Methods: Demographic data, contact history, relapse, localization, tuberculin test, BCG vaccination and treatment duration are evaluated variables. Two groups were created. The first group was diagnosed with head and neck tuberculosis between 2006 and 2011 before the outbreak of the Syrian civil war, and the second group was diagnosed between 2012 and 2017 after the war in Syria caused hundreds of thousands of Syrian citizens to flee their homes and cross the border into Turkey.

Results: Head and neck tuberculosis cases tend to increase after the year of 2012. The number of diagnosed non-Turkish citizens expand after the year of 2012 and reach the highest number in 2017. BCG vaccination status and contact history were found to be the only variables that display statistical significance between the groups.

Conclusions: The number of head and neck tuberculosis cases increased after the Syrian war began due to insufficient rates of vaccination among the Syrian population and this population's overcrowded living environment in Turkey. The burden of these crises affects a region rather than the whole country.

Keywords: head and neck, tuberculosis, lymphadenitis, immigrant

INTRODUCTION

Tuberculosis (TB) is among the oldest infections that remains a major health problem in developing countries. One in every three people in the world is infected with or is at risk of developing TB [1]. According to data released by the World Health Organization (WHO), TB is a major public health problem with 10 million new cases worldwide in 2018 and approximately 1.4 million deaths [2]. TB commonly affects the lungs in 80% of all cases, and extrapulmonary organs are involved in 20% of cases. Extrapulmonary tuberculosis (EPTB), the involvement is direct, through a lymphogenous or hematogenous route from the surrounding tissues [3]. Tuberculosis lymphadenitis (TBLA) is the most common type of EPTB infection, with rates varying between 1.5% and 35% depending on the country [4-6]. However, for head and neck lymph node involvement, infectious, inflammatory and neoplastic diseases such as Squamous cell

carcinoma, lymphoma, other granulomatous and inflammatory processes should not be forgotten in the differential diagnosis. [4,6]. One-sided, multiple lymph nodes between 1.5 cm and 5 cm in diameter in the supraclavicular region characterize the classic presentation of TBLA [7]. Besides, there might be different clinical presentations for different mycobacteria: for instance, structural symptoms like fever, weight loss, fatigue, anorexia, and night sweating occur only in 15–20% of TB cases [8]. Apart from cervical TBLA in the head-neck region, laryngeal (<1%), otic (0.05–0.9%), nasal, pharyngeal, retropharyngeal, and salivary organs may also be infected by TB [9-11]. As TBLA can mimic other pathological conditions, this needs to be considered in the diagnosis and treatment of lymphadenitis [12,13]. The frequency of TB is increasing in geographical areas where social crises occur [14]. Before 2015, the percentage of non-Turkish citizen with TB was 1.3% of total cases in Turkey. The rate of non-Turkish citizen with TB multiplied five times between 2015 and 2018 [15]. There are limited studies on how the distribution of EPTB changed during social crises.

We sought to identify the clinical characteristics of patients diagnosed with head-neck tuberculosis (HNTB), to investigate the number of cases, and to determine whether there were significant changes in our data after immigration from Syria to Turkey between 2011–2017 in the city of Gaziantep, which is next to the war zone on the border with Syria, in the southeastern region of Turkey, and to compare our results with international literature.

MATERIALS AND METHODS

The present study was a single-center descriptive and retrospective study conducted with HNTB cases applying to the Tuberculosis Dispensary between January 2006 and December 2017. Tuberculosis Dispensary is a specific center that keeps records and follow-up and treatment data for all the tuberculosis patients diagnosed in the city. We included 378 adult and pediatric patients diagnosed with HNTB. The diagnosis of TB was made pathologically or microbiologically with biopsy, and we evaluated the ages, genders, nationalities, first admission dates, symptoms, lymphadenopathy characteristics (location, side), accompanying systemic diseases, ear-nose-throat examination notes, presence of TB in history, contact history, Tuberculin Skin Test (TST), Acid Resistance Bacteria smear results, durations, and results of the treatments of the cases. Lung involvement was investigated using lung graphics in all cases. The patient data were obtained from the dispensary archive files.

Main Points;

- Head and neck tuberculosis numbers increases in our region after the beginning of the Syrian war
- Tuberculous lymphadenitis was the most common form of HNTB with a right side superiority.
- Patient family contact is found to be statistically significant refugees or socioeconomically low-level local people live in crowded areas
- Low rates of BCG vaccination is risk factor for the occurence of head and neck tuberculosis.
- Isolation of Tuberculosis patients and vaccination of all newborns may contribute to protection against the occurrence of head and neck tuberculosis.

Randomisation

After identifying the numbers of TBLA cases after the Syrian crisis, we divided them into two groups delineated by the onset of the Syrian civil war and the resulting arrival in Turkey of refugees from Syria.

The first group (group 1) included patients diagnosed with HNTB between 2006 and 2011 who were citizens of the Republic of Turkey (RT). The second group (group 2) of HNTB patients included those diagnosed between 2012 and 2017 including non-Turkish and Turkish citizens.

Ethical Considerations

Before the study began, we obtained approval from the Ethics Committee of Clinical Research at Gaziantep University (2018/95), and the necessary institutional permissions were obtained from the Gaziantep Provincial Health Directorate.

Data Assessment

The data were recorded and analysed by using the SPSS 21 Software Program (SPSS Ltd, Chicago, Illinois, the USA). The normality of the data was determined using the Kolmogorov-Smirnov Test. The numeric data were defined as median, frequency, percentages, and standard deviation. The comparison of numeric values between the groups was determined using the Student-t Test in independent samples and the difference among the categorical data was determined with the Chi-Square Test. The significance level was determined as $p< 0.05$.

RESULTS

A total of 378 patients diagnosed with HNTB presented to the Tuberculosis Dispensary during the 12-year study period. The

patients were divided into two groups based on two periods, the beginning of the Syrian conflict (2006–2011) and after the start of the Syrian conflict (2012–2017). Group 1 had 169 patients and Group 2 had 209 patients. Figure 1 shows the total number of HNTB patients diagnosed annually. In group 1, the highest number of diagnoses was in 2007 (40 patients). However, in group 2, 50 patients were diagnosed with HNTB in 2012. In addition, the largest number of non-Turkish citizens (six Syrian national patients) was diagnosed in 2017.

Group 1 consisted of 52 males (30.8%) and 117 females (69.2%). There were 66 males (31.6%) and 143 females (68.4%) in group 2. When evaluated according to age, the mean age was 40.01±18.12 years (min 1; max 86) in group 1 and 38.21±20.22 years (min 1; max 91) in group 2. Diabetes mellitus, hypertension, and hepatitis B were the commonest additional diseases in both groups. All the patients in group 1 were Turkish citizens and in group 2, 25 patients were non-Turkish citizens (23 were Syrian citizens, one was a citizen of the United Kingdom, and one was a citizen of Azerbaijan). The commonest complaints were neck swelling, headache, and neck pain.

Treatment of 152 (89.9%) patients in this study resulted in cure, and 7 patients (4.1%) died during treatment (Table 1).

Table 1. Evaluation of the treatment results of the patients included in the study

Treatment Results	n (%)
Misdiagnosis	1 (0.6)
Transfer to another city	3 (1.8)
Cure	152 (89.9)
Abandoning the Treatment	6 (3.6)
Death	7 (4.1)
Total	169 (100)

When the treatment results were examined, it was determined that four (%57.1) of the 7 patients who died had lymph node involvement, and the other three (%42.9) were TB patients with central system involvement. It was determined that three (25%) of 12 patients with central system involvement died, and the highest death rate among TB localizations was found to be TB with central involvement (Table 2).

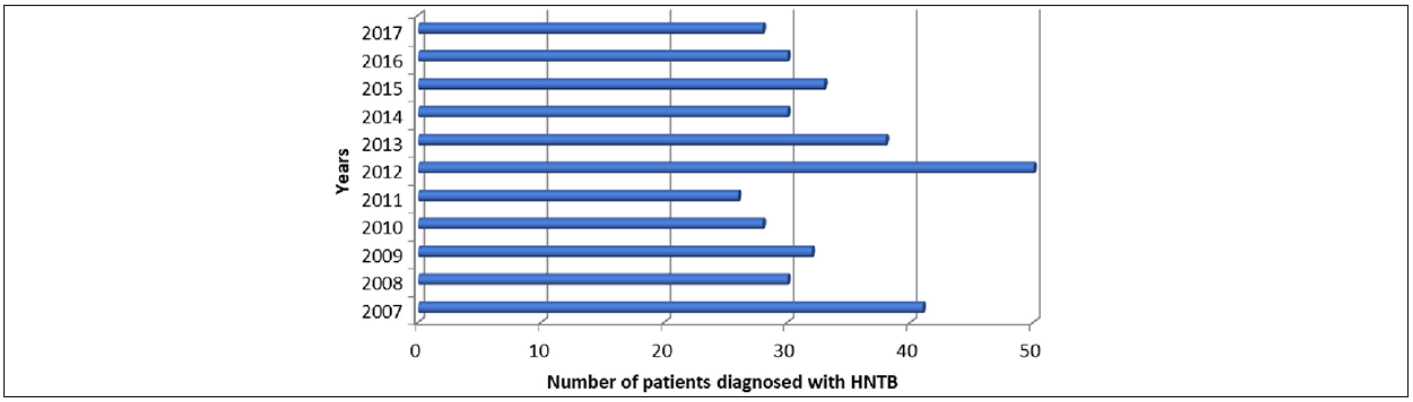

Figure 1. Number of patients diagnosed with Head and Neck Tuberculosis (HNTB) by years

Table 2. Treatment results according to location of disease

Location of Disease	Treatment results					
	Misdiagnosis	Transfer to another city	Cure	Abandoning the Treatment	Death	Total
Skin TB	-	-	1	-	-	**1**
Larynx TB	-	-	3	-	-	**3**
Lymph node TB	1	2	134	6	4	**147**
Orbita TB	0	-	2	-	-	**2**
Parotis TB	0	-	2	-	-	**2**
Parotis and lymph node combined TB	0	-	1	-	-	**1**
Meningitis TB	0	1	8	-	3	**12**
Thyroid TB	0	-	1	-	-	**1**
Total	**1**	**3**	**152**	**6**	**7**	**169**

Presence of Contact

The contact history is history of contact with a patient diagnosed with TB. Twenty-one of 148 patients had a contact history in group 1, meanwhile 47 of 148 patients had a contact history in group 2. This difference was significant between the two groups. Within the family, 16 patients had a contact history in group 1 and 31 patients in group 2, and this was statistically significant (p = 0.012).

Relapse Status

When the recurrence status was evaluated, group 1 had 163 patients admitted for the first time and six patients admitted with a recurrence of TB, and 201 patients were new in group 2 and eight patients had relapses (p = 0.486).

Superiority of Direction and Localization

Concerning the location of lesions, 52% of patients in group 1 and 60.5% of patients in group 2 had it in the right.

When classified according to anatomical localization, the most common is cervical lymphadenitis with a total of 325 patients (86%) of the 378 patients diagnosed with HNTB. There was central nervous system involvement in 27 patients (7.1%), orbital involvement in seven patients (1.9%), larynx involvement in five patients (1.3%), parotid involvement in five patients (1.3%), and other involvements (thyroid, skin, tongue, nasopharynx, oral cavity and maxillary sinus) in nine patients (2.4%) (Figure 2).
When evaluating the localization of lymph nodes, we found that although lymph nodes were more common in the supraclavicular and submandibular regions, there were no significant differences in lymph node localizations (p = 0.162).

Tuberculin Skin Test (Tst) and Bacillus Calmette Guèrin (BCG) Vaccination Scar

We could obtain the TST results of 153 patients. The mean TST was 15.82±6.53 (min 0; max 35) mm in group 1 and 17.21±6.67 (min 0; max 32) mm in group 2, with no statistically significant difference (Student-*t* test p = 0.201).

When the records on scar tissue showing the BCG vaccination were examined, we found that 55 patients in group 1 lacked information, while 90 patients had scars and 24 had no BCG scars. In group 2, 46 patients lacked the scar tissue records, 104 patients had scar tissue, and 59 patients did not have a BCG scar. Evaluating the presence of scars in accordance with nationalities, that of 99 RT citizen patients was not known, 189 patients had scar tissues, and 65 patients did not have them. In non-RT citizen patients, that of two patients was unknown, five patients had scar tissues, and 18 patients did not have BCG scars. We found a significant difference in the vaccination rates when independently evaluating the groups and nationalities (p = 0.018).

Treatment Duration and Result

Concerning the treatment durations, the mean treatment duration in group 1 was 9.32±3.45 months (min 1; max 18) and 8.64 ± 3.47 months (min 1; max24) in group 2, with no significant difference. We found no significant differences when comparing the treatment success rates between the two groups (p = 0.361). Based on the duration of the treatments (nine months or more), 109 (64%) patients in group 1 and 122 (58%) patients in group 2 received adequate treatment, with no statistically significant differences (p = 0.225).

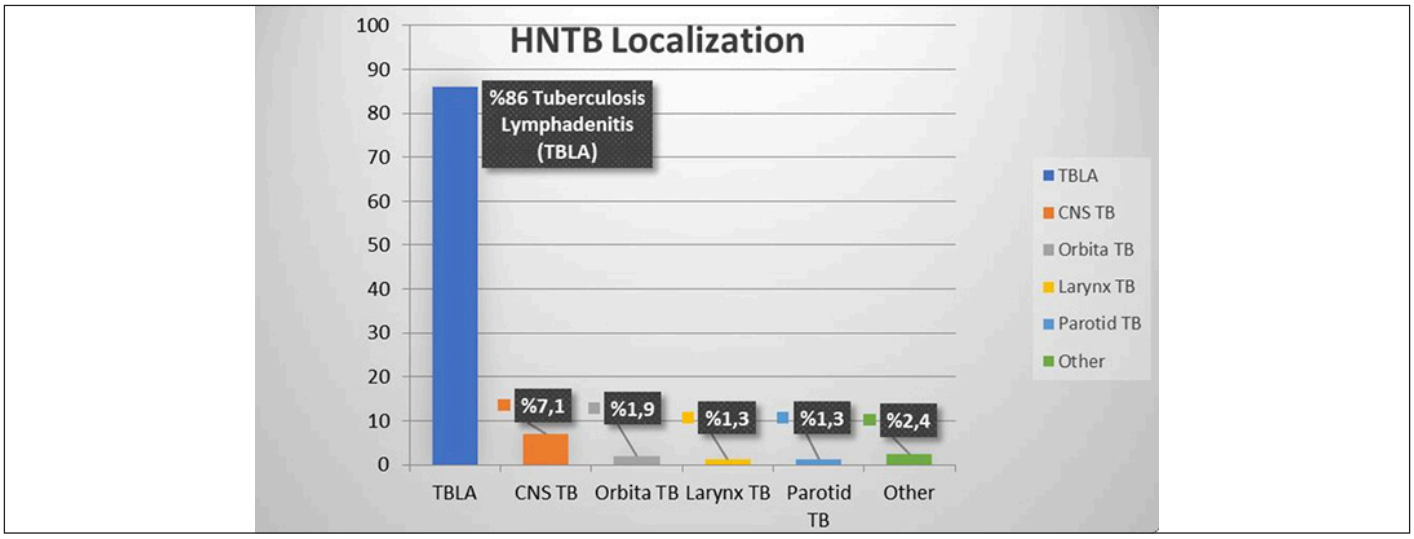

Figure 2. Head and Neck Tuberculosis (HNTB) localization percentages

We found differences between the recommended treatment times because the patients referred from the different healthcare centers. The treatments were given in different ways; the standard four-course treatment with Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E) for the first two months and then binary treatment (HR) for four months, seven months, and 10 months.

DISCUSSION

Tuberculosis is a leading cause of mortality and morbidity worldwide. The spread of this fatal disease increases in crisis-affected populations. The ongoing Syrian civil war has led to significant damage to the national healthcare system and forced millions of Syrians to take refuge in neighboring countries, where the majority face miserable conditions. These circumstances increase the risk of TB development and spreading among Syrian refugees and their host communities. After the beginning of the Syrian crisis in 2011, a remarkable increase in TB cases was reported in countries bordering Syria and is essentially attributed to the massive displacement of the SR population [16]. There is an increased risk for TB disease due to the widespread unhealthy conditions in which the majority of refugees live. Three out of four refugees who live outside the refugee camps stay in very crowded places with more than six people [17]. Vaccination rates are found to be lower among refugees who live outside the camps [18].

Furthermore, these groups are more vulnerable to the extrapulmonary dissemination of TB [19]. In our study, we found that Syrian refugees in Gaziantep have the same situation and living conditions.

Tuberculosis is a preventable infectious disease that is caused by the respiratory transmission of "Mycobacterium tuberculosis" and can spread to all organs by lymphohematogenous route [20]. Having a history of tuberculosis lymphadenitis or sharing the same environment with people who have had TB is a risk factor [21]. Nalini and Vinayak found a history of contact in 9% of patients [10]. The contact rates in HNBT patients in this study is in line with that in the literature. Moreover, in terms of TB transmission, we found that rather than the nationality of the patient, the family contact is statistically significant. Refugees or socioeconomically low-level local people live in crowded areas in which TB is easily spread; this may be the reason why the family contact history was statistically significant in our study groups. We evaluated various variables between two groups and the presence of contact and vaccination were found to be statistically significant in the assessment of HNTB.

Although the efficacy of the BCG vaccine continues to be controversial, live attenuated BCG is still the only vaccine in use for the prevention of TB in humans. It is effective against the severe forms of TB and its use prevents a large number of deaths that would otherwise be caused by TB every year [22]. The rate of BCG vaccine protection in adults aged over 18 years in Turkey was 72.7% and 85% in children aged 0–6 years [23]. The administration of the BCG vaccine in newborns is associated with a lower mortality and morbidity in children under five years of age [24]. EPTB is very common in patients who have not had the BCG vaccine [25]. BCG vaccination rates between 2011 but 2018 did not change in Turkey and decreased year-by-year in the Syrian Arab Republic [26].

In our study, when evaluating patients after 2011, we found that the vaccination rates had decreased; this could be because the migrant patients had not been vaccinated before. Based on these data, it is possible to argue that HNTB may be seen more frequent in unvaccinated TB patients.

HNTB frequently presented as cervical lymphadenopathy in previous studies [9,11,27]. Sayın et al. reported that TBLA (85.4%) was the most frequent HNTB presentation form and right-side involvement was more frequent [11]. In our study, TBLA (86%) was the most common form of HNTB with a right-side prevalence. TBLA involves mostly posterior and supraclavicular lymph nodes [9,27]. Ammari et al. indicated that the deep cervical region had highest number of TBLA (54%) [28]. Nalini and Vinayak [10], on the other hand, found a higher posterior cervical involvement (76%), and found that most patients had a lymphadenopathy of less than 3 cm. Baskota et al. [29] found 51% of TBLA in the posterior triangle, 48% in the upper jugular region, and 36% in the submandibular region. In their study, Sayın et al. [11] found the most frequent involvement (53.6%) in the rear angle. In our study, TBLA was seen in the posterior cervical region, especially in the supraclavicular area and in the submandibular region.

Since the introduction of the tuberculin skin test (TST) also known as the Mantoux test in 1890, it has been widely used for the initial diagnosis of patients suspected of TB and to detect latent infections [30]. TST positivity was reported at a rate of 50% in TBLA patients [31]. When evaluating the 153 patients

with TST results, we found that the average TST in group 1 was 15.8 mm and in group 2 was 17.2 mm. Since atypical TB bacillus is more frequent in children, there is a high risk of false positivity in the tuberculin test. Although it is highly positive in patients with neck masses, a remarkable number of researchers state that the tuberculin test is the first examination method to be used due to its simplicity and low cost [32]. It is considered with an induration of 15 mm or more in those with the BCG vaccine and 10 mm or more in those who do not have the BCG vaccine [23]. We detected 57 patients (61%) in group 1 and 44 patients (72.1%) in group 2 as positive in our study. Although it was not statistically significant, there was an increase in terms of both TST positivity and induration width in group 2.

CONCLUSION

The number of HNTB increased in the Gaziantep province after the beginning of the Syrian war. The risk factors for the occurrence of HNBT include living in a crowded place and lower rates of BCG vaccination may have a greater significance in terms of risk factors than the lymph node location, side, tuberculin skin test result, and nationality. Isolation of TB patients and vaccination of all newborns may contribute to protect against HNTB.

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Conflict of Interest: The authors declare that they have no competing interests.

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Informed Consent: Informed voluntary consent form was prepared due to the nature of the study, ethics committee approval and permission were obtained from the provincial health directorate.

Authors' Contributions: Conception: KT, İA, SA; Design: KT, İA, SA; Supervision: SA; Fundings: SA; Materials: KT; Data Collection and/or Processing: İA, SA; Analysis and/or lnterpretation: AY; Literature Review: AY; Writing: AY; Critical Review: KT, İA, AY, SA.

Ethics Committee Approval: The study was approved by the Ethics Comittee of the Faculty of Medicine of Gaziantep University (2018/95). The study followed the Declaration of Helsinki.

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Original Research

Predictive Risk Factors for Clinically Related Pancreatic Fistula After Pancreaticoduodenectomy: Analysis of 248 Patients

Feyyaz Güngör[1], Arif Atay[2], Nihan Acar[2], Halis Bag[2], Emine Ozlem Gur[2], Osman Nuri Dilek[2]

[1] Department of General Surgery, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey
[2] Department of General Surgery, Faculty of Medicine, Izmir Katip Çelebi University Atatürk Training and Research Hospital, Izmir, Turkey

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Correspondence
Feyyaz Gungor, MD, General Surgical
Address: Department of General Surgery, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey
E-mail: feyyaz.gngr@gmail.com

ABSTRACT

Objective: Postoperative pancreatic fistula (POPF) affects 13-50% of patients undergoing pancreaticoduodenectomy (PD), and remains the main source of post-PD morbidity and mortality. Therefore, determining predictive risk factors for POPF remains popular today. This study aimed to determine the predictive risk factors for clinically related postoperative pancreatic fistula (CR-POPF) in the preoperative and early postoperative period in patients that underwent PD.

Methods: This is a retrospective study involving 248 patients who underwent PD between January 2015 and December 2019 in our center. We compared the groups that did and did not develop CR-POPF. We determined the risk factors affecting CR-POPF by stepwise logistic regression analysis.

Results: 141 (56.8%) of the patients included in the study were male, and the median age was 63 (56-70)/year. The CR-POPF rate was 18.1%. We found a statistically significant difference ($p < 0.05$) in the following parameters: diabetes, smoking, preoperative leukocyte, preoperative neutrophil, postoperative first day (POD1) amylase, POD1 AST, POD1 ALT, POD1 CRP, POD1 lymphocyte-CRP ratio (LCR), postoperative third day (POD3) lymphocyte, POD3 CRP, in POD3 neutrophil-lymphocyte ratio, POD3 platelet-lymphocyte ratio (PLR), POD3 AST-ALT ratio, POD3 LCR, surgeon experience, incision type, Wirsung diameter, pancreatic tissue and operation time. In the stepwise logistic regression model, we found POD1 AST, POD3 CRP, POD3 TLR, diabetes, surgeon experience, and Wirsung diameter as predictive risk factors.

Conclusions: Despite some new methods to reduce the occurrence of POPF, the expected improvement in POPF rates is elusive. Predictive risk factors for POPF may also vary because the response of patients to trauma varies and the postoperative period is very dynamic. In our study, we found POD1 AST, POD3 CRP, POD3 TLR, diabetes, surgeon experience and Wirsung diameter as predictive risk factors for CR-POPF.

Keywords: pancreaticoduodenectomy, pancreatic fistula, predictive, risk factor

INTRODUCTION

In the United States of America, approximately 57,600 people are expected to develop exocrine pancreatic cancer per year and more than 90% of them are expected to die from this disease [1]. The only potential curative treatment of cancers originating in the periampullary region (pancreatic head, ampulla of Vater, distal bile duct and duodenum) is pancreaticoduodenectomy (PD). Postoperative pancreatic fistula (POPF) affects 13-50%

of patients undergoing surgical resection and remains the main source of morbidity and mortality after pancreatic resection [2-4]. POPF is associated with fatal complications such as intraabdominal sepsis and hemorrhage. The literature indicates that mortality develops in 1% of all POPF patients and 25.7% of grade C POPF patients [5]. Despite numerous studies describing new methods to reduce the occurrence of POPF, there has been no significant improvement in POPF rates in the last three decades.

Until recently, literature data regarding the definition and classification of POPF were very heterogeneous. In 2005, the International Study Group of Pancreatic Surgery (ISGPS) developed a consensus definition, which facilitated the adoption of a common language in subsequent studies [6]. This definition was revised in 2016 to limit POPF reporting only to factors affecting the clinical course [2]. With the provision of a common language, studies of determining predictive risk factors for POPF have gained more importance and speed.

In this study, we aimed to determine the predictive risk factors for clinically related postoperative pancreatic fistula (CR-POPF) in the preoperative and early postoperative period in patients that underwent PD.

Main Points;

- POPF is a significant complication after PD and is associated with high morbidity and mortality rates.
- This study aimed to identify predictive risk factors for CR-POPF in the preoperative and early postoperative period in patients who underwent PD.
- The incidence of CR-POPF was 18.1% in the study population. Diabetes mellitus, surgeon experience of less than 10 years in pancreatic surgery, Wirsung diameter <4mm, POD1 AST <69 U/L, POD3 CRP >17.95 mg/dL, and POD3 PLR <225.18 were identified as predictive risk factors for CR-POPF.
- Other factors such as smoking, midline incision, soft pancreatic tissue, and prolonged operation time were associated with increased risk of CR-POPF, but did not reach statistical significance in the logistic regression analysis.
- The study highlights the importance of identifying predictive risk factors for CR-POPF to guide treatment decisions, surgical techniques, and postoperative management to reduce the incidence and complications of POPF.
- Further studies with larger sample sizes and multicenter collaborations are needed to validate these findings and optimize strategies for preventing and managing CR-POPF after PD.

MATERIALS AND METHODS

Data from 320 patients who underwent pancreatic surgery in the General Surgery Clinic of Izmir Katip Çelebi University Atatürk Training and Research Hospital between January 2015 and December 2019 were retrospectively evaluated.

Inclusion criteria in the study:

- Patients undergoing a PD procedure
- Patients whose records are fully accessed from the hospital database

Exclusion criteria in the study:

- Patients undergoing pancreatic surgery other than PD procedure
- Patients undergoing other surgical procedures in addition to the PD procedure

Two hundred forty-eight patients who met these criteria were included in the study, and written informed consent was obtained from all patients. The study started with the approval of the ethics committee of our center with approval number 883, and all steps were carried out in accordance with the principles of the Declaration of Helsinki.

Definition of CR-POPF and Clinical Variables

POPF was defined according to the ISGPS 2016 updated consensus report [2]. The evaluated criteria were analysed according to the groups that did and did not develop CR-POPF (Grade B and C).

The analysis covers demographic data, comorbidities, preoperative biliary drainage status (internal and external), blood parameters (preoperative, intraoperative and postoperative), tumor localization, surgical technique, intraoperative findings, histopathological diagnoses, morbidity and mortality of the patients included in the study. As blood parameters, the hemogram and biochemistry parameters of the patients in the week before surgery, on the first postoperative day and on the postoperative third day, as well as the pH and lactate parameters in the intraoperative second-hour arterial blood gas were analyzed.

As intraoperative parameters, surgeon's experience (<10 years and >10 years), incision type, surgical technique, structure of pancreatic tissue (soft and hard), Wirsung diameter (<4mm and >4mm), vascular resection status, pancreaticojejunostomy

(PJ) technique, blood transfusion need and operation time were analyzed.

Delayed gastric emptying, post-PD hemorrhage and bile leakage were done according to international definitions. Delayed gastric emptying, post-PD hemorrhage, surgical site infection, bile leakage, need for reoperation, need for intensive care follow-up, early mortality and length of hospital stay were analyzed.

Surgical Technique and Follow-up

In our center, surgical techniques were personalized on a patient basis by three different surgical teams. Conventional (classical PD and pyloric-sparing PD) surgery was performed in all patients. All patients had undergone PJ as pancreatic enterostomy. Jackson-Pratt drains were placed under PJ and HJ anastomoses in all patients. The drain was terminated on the third postoperative day after confirmation that the drain amylase was within normal limits. Prophylactic somatostatin analogs were not given to any patient. Frequent vital and inflammatory markers were followed up in patients with POPF. Imaging methods were used in cases in which intraabdominal loculated fluid or abscess was suspected. If loculated fluid or abscess was detected, depending on the size or location of the fluid, conservative and percutaneous drainage methods were preferred primarily.

Statistical Analysis

The data were evaluated using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) statistical package program. Descriptive statistics were given as unit number (n), percentage (%), median (M), 25th percentile (Q1), 75th percentile (Q3), mean and standard deviation. Independent samples t-test, Mann-Whitney U test, Pearson chi-square, Fisher-exact test and Fisher Freeman Halton test were used for comparisons between groups that did / did not develop CR-POPF. Receiver Operating Characteristic (ROC) analysis was performed to determine the cut-off value of metric values with statistical significance. Risk factors affecting CR POPF were determined by stepwise logistic regression analysis. The OR values and 95% confidence intervals of the risk factors were specified. $p < 0.05$ was considered statistically significant.

RESULTS

141 (56.8%) of the 248 patients included in the study were male and the median age was 63 (56-70)/year. 21 (8.5%) patients had a biochemical leak, 41 patients (16.5%) had Grade B, and 4 (1.6%) patients had Grade C POPF. The CR-POPF rate was 18.1%. In the evaluation of the demographic characteristics and comorbidities of the patients, the detection of more CR-POPF in the patient group with diabetes mellitus was found to be statistically significant ($p = 0.044$). In addition, less CR-POPF developed in the smoking group, and the difference between the groups was statistically significant ($p = 0.021$). Preoperative biliary drainage (PBD) was applied to 146 (58.8%) patients. It was detected that PBD was applied more in the group with CR POPF, but there was no statistical difference between the groups ($p = 0.401$) (Table 1).

In the evaluation of preoperative laboratory parameters, it was found that the group with CR-POPF had higher lymphocyte and neutrophil values, and the difference between the groups was statistically significant (p-value, respectively; 0.042, 0.022) (Table 2). In the evaluation of intraoperative parameters, more CR-POPF was observed in the patient group operated by surgeons with less than 10 years of experience in pancreatic surgery, and the difference was statistically significant ($p < 0.001$). More CR-POPF was observed in the patient group operated with midline incision and the difference between the groups was statistically significant ($p = 0.002$). Wirsung diameter <4mm and soft pancreatic tissue were more common in the CR-POPF group. The difference between the groups was statistically significant (p-value, respectively; <0.001, 0.003). In addition, the operation time was longer in the group with CR-POPF and the difference was statistically significant ($p = 0.03$) (Table 3).

In the comparison of the laboratory parameters on the postoperative first day between the groups, amylase and CRP values were higher; while AST, ALT and lymphocyte-CRP ratios (LCR) were lower in the group with CR-POPF. The difference was statistically significant between groups (p-values, respectively; 0.004, 0.005, 0.012, 0.006, and 0.005) (Table 2). In the comparison of the groups according to the laboratory parameters on the postoperative third day, it was found that CRP, neutrophil-lymphocyte ratio (NLR), thrombocyte-lymphocyte ratio (PLR) and AST-ALT ratio were higher, while lymphocytes and LCR were lower in the group with CR-POPF. The difference between the groups was statistically significant (p-values, respectively; $p<0.001$, $p<0.001$, $p=0.001$, $p=0.016$, $p<0.001$, and $p<0.001$) (Table 2). Surgical site infection, delayed gastric emptying, reoperation, Clavien Dindo ≥3a complications were found to be more common in the group with CR-POPF. In addition, the patients stayed longer in the hospital and the

difference between the groups was statistically significant (p value, respectively; p<0.001, p<0.001, p=0.005, p<0.001, p<0.001) (Table 4). On the other hand, there was no statistically significant difference between the groups in terms of 30-day mortality (p = 0.780).

Cut-off values for metric variables with statistically significant differences between groups were determined by ROC analysis (Table 5). Metric variables were categorized as being below and above the specified cut-off values.

The stepwise logistic regression model was used to determine predictive risk factors for CR-POPF. In the stepwise logistic regression model, diabetes mellitus, smoking, preoperative leukocyte, preoperative neutrophil, postoperative first day (POD1) amylase, POD1 AST, POD1 ALT, POD1 CRP, POD1 LCR, third postoperative day (POD3) lymphocyte, POD3 CRP, POD3 NLR, POD3 PLR, POD3 AST-ALT ratio, POD3 LCR, surgeon experience, incision type, Wirsung diameter, pancreatic tissue and operation time were included. The logistic regression model obtained in step 13, the last step, was statistically significant (p <0.001). It was observed that POD1 AST <69 U/L increases the CR-POPF risk 3.168 times. Similarly, POD3 CRP >17.95 mg/dL increases the risk of CR-POPF 4.871 times and POD3 TLR <225.18 increases it 3.338 times. Having diabetes mellitus as a comorbidity increases the risk of CR-POPF 2.407 times. If the surgeon's experience of pancreatic surgery is less than 10 years, the risk of CR-POPF increases 7,663 times. Wirsung diameter <4 mm increases the risk of CR-POPF by 9.945 (Table 6).

Table 1. Demographics for patients with and without CR-POPF

	Total (n=248)	No CR POPF (n=203)	CR POPF (n=45)	p value
Male sex$^{\beta}$	141 (56.8)	114 (56.2)	27 (60)	0.638*
Age$^{\alpha}$ (years)	63 (56-70)	63 (56-70)	61 (58-66)	0.347$^{\#}$
Diabetes mellitus$^{\beta}$ (Yes)	94 (37.9)	71 (35)	23 (51.1)	**0.044***
Hypertension$^{\beta}$ (Yes)	85 (34.2)	65 (32)	20 (44.4)	0.112*
Heart disease$^{\beta}$ (Yes)	59 (23.7)	46 (22.7)	13 (28.9)	0.375*
Pulmonary disease$^{\beta}$ (Yes)	30 (12)	26 (12.8)	4 (8.9)	0.466*
Smoking$^{\beta}$ (Yes)	54 (21.7)	50 (24.6)	4 (8.9)	**0.021***
ASA$^{\beta}$ ≥3	89 (35.8)	71 (35)	18 (40)	0.525*
CCI$^{\beta}$ ≥5 points	135 (54.4)	109 (53.7)	26 (57.8)	0.619*
PBD$^{\beta}$ (Yes)	146 (58.8)	117 (57.6)	29 (64.4)	0.401*

$^{\alpha}$; median (IQR), $^{\beta}$; numbers (%),*; Chi-square, $^{\#}$; Mann–Whitney U-test
ASA; physical status classification system by the American Society of Anesthesiologists, CCI; Charlson Comorbidity Index, PBD; preoperative biliary drainage

Table 2. Preoperative and postoperative laboratory data for patients with or without CR-POPF

	No CR POPF (n=203)	CR POPF (n=45)	p value
Preoperative			
Leukocyte$^{\alpha}$ (10^9/L)	7.4 (6.1-9.2)	7.8 (6.9-10.2)	**0.042**$^{\#}$
Hemoglobin^{b} (g/dL)	12.16±1.74	11.93±1.75	0.441*
Neutrophil$^{\alpha}$ (10^9/L)	4.6 (3.5-5.9)	5.2 (4.4-6.6)	**0.022**$^{\#}$
Lymphocyte$^{\alpha}$ (10^9/L)	1.8 (1.3-2.3)	1.8 (1.4-2.3)	0.313$^{\#}$
Platelet$^{\alpha}$ (10^9/L)	270 (217-340)	301 (249-335)	0.134$^{\#}$
MPV$^{\alpha}$ (fL)	10.5 (9.8-11.5)	10.6 (9.9-11.7)	0.652$^{\#}$
Amilaz$^{\alpha}$ (U/L)	67 (46-97)	55 (42-99)	0.376$^{\#}$
AST$^{\alpha}$ (U/L)	40 (22-83)	38 (19-76)	0.231$^{\#}$
ALT$^{\alpha}$ (U/L)	55.5 (24-113)	52 (20-105)	0.403$^{\#}$

	TB[α] (mg/dL)	2.6 (0.8-7.3)	2.3 (0.6-5)	0.483[#]
	DB[α] (mg/dL)	1.8 (0.4-5)	1.4 (0.3-4)	0.461[#]
	CRP[α] (mg/L)	1.40 (0.4-3.26)	2.5 (0.7-3.4)	0,189[#]
	Ca 19-9[α] (U/mL)	43 (15-214)	25.5 (11-84)	0.094[#]
	NLR[α]	2.46 (1.8-3.8)	2.77 (2-4.1)	0.363[#]
	PLR[α]	157.14 (112.8-229)	152.78 (120.5-195.8)	0.777[#]
	LCR[α]	1.08 (0.4-3.8)	0.91 (0.4-3)	0.713[#]
POD1				
	Leukocyte[α] (10^9/L)	14.59 (11.5-17.2)	14.95 (12.2-19.1)	0.222[#]
	Hemoglobin[b] (g/dL)	11.67±1.48	11.79±1.59	0.620[*]
	Neutrophil[α] (10^9/L)	12.63 (10-15.2)	13.36 (10.9-16.5)	0.128[#]
	Lymphocyte[α] (10^9/L)	0.85 (0.6-1.3)	0.72 (0.6-1.3)	0.743[#]
	Platelet[α] (10^9/L)	278 (213-354)	299 (244-368)	0.140[#]
	Amilaz[α] (U/L)	176 (46-176)	176 (87.5-339.5)	**0.004**[#]
	AST[α] (U/L)	83 (48-139)	52 (37.5-89.5)	**0.005**[#]
	ALT[α] (U/L)	84 (47-149)	65 (34.5-89.5)	**0.012**[#]
	TB[α] (mg/dL)	2.23 (1-4.2)	1.56 (0.9-3.6)	0.284[#]
	DB[α] (mg/dL)	1.6 (0.5-3)	0.80 (0.5-2.5)	0.190[#]
	CRP[α] (mg/L)	10.29 (5.9-14.8)	13.87 (9.1-20.4)	**0.006**[#]
	NLR[α]	13.98 (9.5-21.7)	17.70 (10.9-21.9)	0.169[#]
	PLR[α]	325 (216-470)	386.46 (227.8-568.3)	0.147[#]
	LCR[α]	0.09 (0.1-0.2)	0.06 (0.03-0.1)	**0.005**[#]
	AST-ALT ratio[α]	0.97 (0.8-1.3)	1.02 (0.8-1.3)	0.497[#]
POD3				
	Leukocyte[α] (10^9/L)	12.08 (9.6-14.4)	11.76 (9.2-16.3)	0.729[#]
	Hemoglobin[b] (g/dL)	9.88±1.26	9.72±1.11	0.424[*]
	Neutrophil[α] (10^9/L)	10.14 (7.6-12.1)	9.99 (7.9-14.4)	0.342[#]
	Lymphocyte[α] (10^9/L)	1.18 (0.9-1.6)	0.84 (0.6-1.2)	**<0.001**[#]
	Platelet[α] (10^9/L)	232 (182-297)	232 (178-266)	0.695[#]
	Amilaz[α] (U/L)	34 (18-52.8)	48 (23.5-59)	0.113[#]
	AST[α] (U/L)	34 (23-58)	33 (24-61)	0.955[#]
	ALT[α] (U/L)	38 (23-75)	37 (21.5-54.5)	0.22[#]
	TB[α] (mg/dL)	1.71 (0.8-3.1)	1.17 (0.8-2.7)	0.415[#]
	DB[α] (mg/dL)	0.99 (0.4-2.1)	0.5 (0.4-1.9)	0.237[#]
	CRP[α] (mg/L)	17.15 (12.1-20.4)	22.39 (17.6-27.5)	**<0.001**[#]
	NLR[α]	8.75 (5.8-12.2)	12.49 (8.5-19.4)	**<0.001**[#]
	PLR[α]	201.64 (146.8-257.7)	276.19 (172.5-386.4)	**0.001**[#]
	LCR[α]	0.07 (0.04-0.1)	0.03 (0.02-0.05)	**<0.001**[#]
	AST-ALT ratio[α]	0.83 (0.6-1.2)	1.02 (0.8-1.3)	**0.016**[#]

[α]; median (IQR), [#]; Mann–Whitney U-test, [*]; Independent samples t test, [b]; mean and standard deviation

POD1; postoperative day 1, AST; aspartate aminotransferase, ALT; alanine aminotransferase, TB; total bilirubin, DB; direct bilirubin, CRP; C-reactive protein, NLR; neutrophil-lymphocyte ratio, PLR; platelet-lymphocyte ratio, LCR; lymphocyte-CRP ratio

Table 3. Intraoperative data for patients with or without CR-POPF

		No CR POPF (n=203)	CR POPF (n=45)	p value
Location[β]	Distal bile duct	16 (7.9)	7 (15.6)	0.253[*]
	Duodenum	7 (3.4)	2 (4.4)	
	Head of pancreas	77 (37.9)	11 (24.4)	
	Ampulla vateri	93 (45.8)	22 (48.9)	
	Uncinate process	10 (4.9)	3 (6.7)	
Surgeon experience[β]	<10 years	56 (27.6)	28 (62.2)	**<0.001**[*]
	≥10 years	147 (72.4)	17 (37.8)	
Incision type[β]	Midline	25 (12.3)	14 (31.1)	**0.002**[*]
	Subcostal	178 (87.7)	31 (68.9)	
Surgical technique[β]	Classical	132 (65)	32 (71.1)	0.435[*]
	PPPD	71 (35)	13 (28.9)	
Wirsung diameter[β]	<4 mm	85 (41.9)	37 (82.2)	**<0.001**[*]
	≥4 mm	118 (58.1)	8 (17.8)	
Pancreas texture[β]	Soft	108 (53.2)	35 (77.8)	**0.003**[*]
	Hard	95 (46.8)	10 (22.2)	
PJ technique[β]	Duct to mucosa	134 (66)	27 (60)	0.445[*]
	Others	69 (34)	18 (40)	
Vascular resection[β]	No	188 (92.6)	43 (95.6)	0.745[*]
	Yes	15 (7.4)	2 (4.4)	
Intraoperative transfusion[β]	No	95 (46.8)	19 (42.2)	0.577[*]
	Yes	108 (53.2)	26 (57.8)	
Intraoperative pH[α]		7.41 (7.37-7.45)	7.39 (7.35-7.43)	0.684[#]
Intraoperative laktat[α] (mmol/L)		1 (0.8-1.4)	1.1 (0.9-1.9)	0.119[#]
Operative time[α] (min)		315 (260-359)	330 (300-380)	**0.03**[#]

[α]; median (IQR), [β]; numbers (%),[*]; Chi-square, [#]; Mann–Whitney U-test
PPPD; pylorus-preserving pancreaticoduodenectomy, PJ; pancreaticojejunostomy

Table 4. Postoperative outcome in relation to CR-POPF

	Total (n=248)	No CR POPF (n=203)	CR POPF (n=45)	p value
Histopathology[β] (Adenocarcinoma)	191 (77.01)	161 (79.3)	30 (66.7)	0.068[*]
SSI[β] (Yes)	102 (41.12)	72 (35.5)	30 (66.7)	**<0.001**[*]
DGE[β] (Yes)	61 (24.6)	30 (14.8)	31 (68.9)	**<0.001**[*]
PPH[β] (Yes)	33 (13.3)	25 (12.3)	8 (17.8)	0.329[*]
Biliary leakage[β] (Yes)	7 (2.8)	6 (3)	1 (2.2)	>0.999[*]
Clavien Dindo[β] ≥3a	59 (23.1)	40 (19.7)	19 (42.2)	**0.001**[*]
Reoperation[β] (Yes)	21 (8.5)	12 (5.9)	9 (20)	**0.005**[*]
ICU follow-up[β] (Yes)	60 (24.2)	50 (24.6)	10 (22.2)	0.733[*]
Length of stay[α] (days)	10 (7-15)	9 (7-14)	19 (14-24)	**<0.001**[#]
30-day mortality[β] (Yes)	24 (9.7)	19 (9.4)	5 (11.1)	0.780[*]

[α]; median (IQR), [β]; numbers (%),[*]; Chi-square, [#]; Mann–Whitney U-test
SSI; surgical site infection, DGE; delayed gastric emptying, PPH; post-pancreaticoduodenectomy hemorrhage, ICU; intensive care unit

Table 5. ROC analysis for metric variables with statistically significant differences

		AUC-ROC (%95)	Cut off value	p value	Sensitivity (%)	Specificity (%)
Preoperative						
	Leukocyte (10^9/L)	0.597 (0.508-0.685)	7.65	0.042	53.3	54.2
	Neutrophil (10^9/L)	0.609 (0.522-0.697)	4.85	0.022	55.6	57.1
POD1						
	Amilaz (U/L)	0.635 (0.541-0.728)	174	0.005	60	48.8
	AST (U/L)	0.633 (0.544-0.721)	69	0.005	62.1	62.2
	ALT (U/L)	0.62 (0.533-0.707)	73.5	0.012	58.6	60
	CRP (mg/L)	0.631 (0.538-0.724)	12.35	0.006	57.8	58.6
	LCR	0.633 (0.546-0.720)	0.0781	0.005	60.1	60
POD3						
	Lymphocyte (10^9/L)	0.683 (0.593-0.774)	0.95	<0.001	64.4	65
	CRP (mg/L)	0.716 (0.632-0.801)	17.95	<0.001	66.7	67.5
	NLR	0.696 (0.608-0.784)	10.26	<0.001	64.4	63.5
	PLR	0.658 (0.561-0.756)	225.18	0.001	64.4	64.5
	AST-ALT ratio	0.615 (0.525-0.705)	0.94	0.016	60	60.1
	LCR	0.743 (0.659-0.827)	0.052	<0.001	68.9	68
Operative time (min)		0.603 (0.515-0.691)	329.5	0.03	55.6	55.7

AUC; area under curve, POD1; postoperative day 1, AST; aspartate aminotransferase, ALT; alanine aminotransferase, TB; total bilirubin, CRP; C-reactive protein, NLR; neutrophil-lymphocyte ratio, PLR; platelet-lymphocyte ratio, LCR; lymphocyte-CRP ratio

Table 6. Analysis to identify risk factors for CR-POPF

		OR	95% CI	p value
Step 13	POD1 AST <69 U/L	3.168	1.293-7.764	**0.012**
	POD3 CRP >17.95 mg/L	4.871	2.013-11.787	**<0,001**
	POD3 PLR <225.18	3.338	1.417-7.863	**0.006**
	POD3 AST-ALT ratio <0.94	2.031	0.868-4.751	0.102
	Diabetes mellitus (Yes)	2.407	1.019-5.687	**0.045**
	Surgeon experience <10 years	7.663	3.082-19.050	**<0,001**
	Wirsung diameter <4 mm	9.945	3.580-27.631	**<0,001**

POD1; postoperative day 1, POD3; postoperative day 3, CRP; C-reactive protein, PLR; platelet-lymphocyte ratio

DISCUSSION

One of the most important causes of morbidity and mortality after PD is POPF. It is the most common mortal complication regardless of the surgical procedure type. POPF causes life-threatening (at a rate of 40%) intraabdominal abscesses and PPH [2,7,8]. In our study, CR-POPF was found to be associated with surgical site infection, delayed gastric emptying, reoperation, ≥3a morbidity according to Clavien Dindo classification and long hospital stay. Although CR-POPF is not associated with early mortality, it will cause a delay in adjuvant therapy and a decrease in long-term survival. Therefore, anticipating or early detecting CR-POPF before it develops is very important for treatment modifications.

Knowing the risk factors for POPF after PD can provide more enlightening information to the patients in the preoperative period and can contribute to more accurate operation decisions in borderline respectable patients. In addition, surgical techniques and postoperative management can be reviewed depending on the potential risk of developing POPF. For example; for a patient with a high risk of POPF, different options such as pancreaticoenterostomy techniques, internal or external stenting during PJ anastomosis, or feeding jejunostomy may be considered. Also, prophylactic somatostatin analogs can be added to the postoperative treatment algorithm. In the group with low risk of POPF, drains may not be used and accelerated

treatment protocols may be considered.

Whether diabetes mellitus is, a risk factor for POPF is controversial [9-13]. Srivastava et al. [12] and Cheng et al. [13] reported that preoperative diabetes mellitus is a risk factor for POPF after PD. In our study, 51.1% (23 patients) of the patients who developed CR-POPF had diabetes mellitus. In the the analysis, we found a statistically significant difference was found between the groups. In the logistic regression analysis, the patient group with diabetes mellitus as a comorbidity had a 2.407 times higher risk of CR-POPF.

In our study, 66.1% (164 patients) of the patients were operated by surgeons with an experience of more than 10 years of pancreatic surgery. In this group, the incidence of CR-POPF was 10.3%. In the patient group operated by surgeons with an experience of less than 10 years of pancreatic surgery, the incidence of clinically significant CR-POPF was 33.3%. In our study, pancreatic surgery experience less than 10 years was found to be a risk factor for CR-POPF. Søreide et al. concluded in their review that the hospital volume and surgeon experience do not have an effect on CR-POPF, and that CR-POPF rates did not decrease after the centralization of pancreatic surgeons in Sweden and Finland [14]. In their single-center study involving 1003 PD patients, Schmidt et al. defined surgeons who performed 50 or more PD procedures as “experienced” and they reported that less CR-POPF was detected in the experienced surgeon group [15]. Although some studies contend that surgical experience is not related to CR-POPF, our study and other studies in the literature point out surgical experience as one of the most important criteria for both CR-POPF and surgical success.

There is no literature focusing on the relationship between incision type and CR-POPF. Although the shape of the incision varies due to the surgeon’s habit, the incision type is personalized on a patient basis, like all treatment protocols. In our study, more CR-POPF was found in patients with midline incisions. Regression analysis revealed that midline incision is not a risk factor. The reason for the detection of more CR-POPF in midline incision is might be due to the use of the midline incision in the patient group at risk for CR-POPF or to the insufficient exposure in the midline incision, which may affect the quality of the PJ. Although, in our study, a difference was detected between the groups in terms of incision type, the surgeon decides the incision type depending on the patient type. In order to understand the effect of incision shape on CR-POPF, multi-center studies and larger samples are needed.

We found that Wirsung diameter less than 4 mm was a predictive risk factor for CR-POPF and it increased the risk of CR-POPF 9.945 times. In many studies, soft pancreatic tissue and the non-dilation of the Wirsung duct were found to be associated with CR-POPF [14,16-21]. However, in our study, more CR-POPF was detected in the patient group with soft pancreatic tissue, while logistic regression analysis revealed that there was no predictive risk factor.

CRP is a valuable marker with a mean half-life of approximately 19 hours. It is used to detect disease activity, inflammatory response, and postoperative recovery [22]. Clinical use of CRP has become routine today. It has been reported that pancreatic necrosis can be detected as high as 95% in acute pancreatitis [22]. However, pathology-specific cut-off values are still subject to studies, and controversial cut-off values are reported [22-24]. In our study, the CRP cut-off value for POD3 was 17.95 mg/L (ROC-AUC 0.716 95% Cl (0.632-0.801), p <0.001). It was found that the risk of CR-POPF increased 4.871 times in the patient group with POD3 CRP> 17.95 mg/L. As in our study, in many other studies, POD3 CRP value was reported to be higher in the group with CR-POPF [23-27].

Very few studies in the literature have assessed whether there is a relationship between AST and CR-POPF, and they detected no relationship [28-30]. While mild levels of AST and ALT are usually detected in some patients after pancreatic surgery, the importance of high or low levels of these values is not clear in the literature. Winter et al. [31] conducted a study in which the data of 2,894 PD patients were evaluated retrospectively. They reported that AST> 187 U/L is associated with mortality. However, this study, did not find a relationship between AST and POPF, either. In our study, we found that the CR-POPF risk increased 3.168 times in the patient group with POD1 AST <69 U/L. Ours is the first study in the literature to find a relationship between POD1 AST value and CR-POPF.

PLR as an inflammatory biomarker has been evaluated in a limited number of studies in terms of complications after pancreatic surgery and CR-POPF, and no significant relationship was detected (29,32). In our study, we found that the relationship with CR-POPF was 3.338 times higher in the patient group with PLR <225.18 on the third postoperative day. In this respect, ours is the first study to find a relationship between POD3 PLR and CR-POPF.

The major limitation of our study is its retrospective nature and small sample size. In addition, the application of PD by different teams and the application of different surgical techniques are other factors that disrupt the homogeneity of the study group. There is a need for more homogeneous, wider and multi-center studies on this subject.

CONCLUSION

Pancreatic fistula is a natural consequence of insufficient control of exocrine secretion following PD. The definition of ISGPS provided a common scientific language for POPF, which deepened the literature knowledge on POPF. However, due to different responses of patients to surgical trauma and the dynamism of postoperative processes, the expected progress has not been achieved in applications required to prevent POPF. In this respect, determining predictive risk factors for POPF is still popular today.

In our study, diabetes mellitus, surgeon having less than 10 years of pancreatic surgery experience, Wirsung diameter <4 mm, POD1 AST <69 U/L, POD3 CRP >17.95mg/L and POD3 PLR <225.18 were found as predictive risk factors for CR-POPF.

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Original Research

The Impact of Cervical Pap Smear on The Prognostic Risk Groups of Endometrial Carcinoma

Ayse Sumeyye Demir Gungor[1], Canan Kabaca[2], Serkan Akis[2], Evrim Bostanci Ergen[3]

[1] Department of Obstetrics and Gynecology, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey
[2] Department of Gynecologic Oncology, University of Health Sciences, Zeynep Kamil Women and Children Diseases Education and Research Hospital, Istanbul, Turkey
[3] Department of Obstetrics and Gynecology, University of Health Sciences, Zeynep Kamil Women and Children Diseases Education and Research Hospital, Istanbul, Turkey

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Correspondence
Ayse Sumeyye Demir Gungor, MD
Address: Department of Obstetrics and Gynecology, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey
E-mail: draysesumeyye@gmail.com

ABSTRACT

Objective: To investigate the importance of preoperative cervical Pap smear in patients with endometrial cancer and the impact of it on the prognostic risk groups of endometrial cancer.

Methods: The preoperative cervical cytology results of 423 patients who underwent staging surgery for endometrial cancer between the years of 2010 and 2020 in the gynecological oncology clinic of the tertiary center were examined in a retrospective observational study. The relations between cervical Pap smear results and pathological prognostic factors of endometrial cancer such as tumor histology, tumor size, FIGO grade, lymphovascular space invasion and FIGO stage were evaluated in detail. The impact of cervical cytology results in the prognostic risk groups (molecular classification unknown) specified in the ESGO/ESTRO/ESP (2020) guideline was also examined. SPSS version 25.0 program was used in the analysis of the data.

Results: Abnormal cervical Pap cytology was present in 12.1% (n= 51) of the patients included in the study. Significantly more abnormal cervical cytology was observed in the high prognostic risk groups (p= 0.017), tumors with non-endometrioid histologic types (p= 0.001), and patients with adnexal involvement (p= 0.007). In the subgroup analysis of endometrioid type endometrial adenocarcinomas, as the FIGO grade increased, the rate of abnormal cervical cytology increased significantly (p= 0.014).

Conclusions: Pre-operative cervical cytology abnormality may predict the need for intra-operative systematic surgical staging and postoperative adjuvant therapy.

Keywords: Endometrial cancer, prognostic risk, cervical cytology, FIGO stage, adjuvant therapy

INTRODUCTION

Pap smear screening tests are widely applied all over the world and provide an opportunity to detect cervical pathologies at an early stage [1]. However, there is currently no standardized effective screening method for endometrial cancer. Anatomically, the continuity of the uterine cavity with the cervix offers the opportunity to examine the endometrial cells shed from the upper genital tract in Pap smear samples. Studies have reported that cytology tests can detect endometrial cancers at a rate of approximately 45% [2]. It is also promising that up to 80% of

endometrial cancer can be detected with new molecular analyzes in Pap smear samples [3]. However, the issue that arouses more curiosity than the diagnostic adequacy of the cytology is whether it has prognostic significance in preoperative and postoperative management of patients with endometrial cancer.

The prognosis is highly dependent on the stage of the disease and tumor histology. Factors such as tumor grade, lymphovascular space invasion (LVSI), myometrial invasion (MI), lymph node involvement, and peritoneal cytology positivity, which can also be obtained from the final pathology reports are effective on the prognosis of the disease. In the ESGO (European Society of Gynecological Oncology)/ESTRO (European Society for Radiotherapy and Oncology)/ESP (European Society of Pathology) guidelines, prognostic risk groups (low, moderate, high-intermediate, high, advanced and metastatic) were established with all these factors and adjuvant treatment according to these prognostic risk groups were reported [4]. The significance of abnormal Pap smear sampling is unknown in the prognostic risk groups. The possible integration of abnormal Pap smear tests to the prognostic risk assessment may open an era for the reorganization of all risk groups in the future.
In this study, our aim is to analyze the correlation between the Pap smear results and the pathological factors and the prognostic risk groups of endometrial carcinoma and discuss it in the light of current literature.

Main Points;

- Abnormal Pap smear results prior to endometrial cancer surgery can predict the need for intraoperative systematic staging and postoperative adjuvant therapy.
- The study evaluated the correlation between preoperative cervical Pap smear results and pathological factors in endometrial cancer, including tumor histology, tumor size, FIGO grade, lymphovascular space invasion, and FIGO stage.
- Abnormal cervical cytology was significantly associated with high prognostic risk groups, non-endometrioid histologic types, and adnexal involvement.
- In the subgroup analysis of endometrioid type endometrial adenocarcinomas, the rate of abnormal cervical cytology increased significantly with higher FIGO grades.
- Pre-operative cervical cytology abnormality may have implications for the selection of intraoperative staging procedures and postoperative adjuvant therapy in endometrial cancer patients.

MATERIALS AND METHODS

Patients (n=733) who were operated for endometrial cancer between the years 2010-2020 were assessed for eligibility to the retrospective observational study. Written informed consent was obtained from all patients included in the study. The study started with the approval of the local ethics committee with the approval number 2021/17 and all steps were carried out in accordance with the principles of the Declaration of Helsinki. The medical records of the patients were accessed by examining the archive module and patient files of the Health Information System.

Cervical samples were taken with an endocervical brush and prepared with the Thin Prep Processor (Cytyc, Boxborough, MA, USA). The samples were examined by the expert gyneco-pathologist at our institute. Cytological evaluations were reviewed according to the Bethesda 2014 system [5]. Smear results which were negative for malignancy and had signs of inflammation and infection were classified in the normal cytology group. All results other than normal cytology were evaluated as abnormal cytology. Endometrial cells over 40 years of age were classified as benign endometrial cells. Patients with insufficient Pap smear results were excluded from the study. In addition, patients with cervical intraepithelial neoplasia (CIN) lesion in the cervix and patients with second primary malignancy were excluded from the study. As a result, 423 patients who had Pap smear results within 6 months before the operation and had adequate surgical staging were included in the study (Fig. 1).

Data from final pathology results, such as tumor size, histopathological type, FIGO grade, MI, cervical stromal involvement, LVSI, lymph node involvement, cytology of peritoneal washing, adnexal involvement, parametrial involvement, FIGO stage, postoperative residual disease, distant metastasis were evaluated. Then, patients were classified into low, moderate, high-intermediate, high, advanced and metastatic risk groups according to the prognostic risk groups (molecular classification unknown) defined in the ESGO/ESTRO/ESP (2020) guidelines [4]. Correlations between the Pap smear results and the pathological factors and the prognostic risk groups of endometrial carcinoma were analyzed.

The data were evaluated by using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) statistical package program. In the tables, continuous variables are presented as mean±standard deviation, while categorical variables are presented as numbers

(N) and percentage (%). Chi-Square test was used to compare categorical variables. Comparisons between groups were made using the Independent Samples T-Test for continuous variables. P<0.05 was considered statistically significant.

RESULTS

The mean age of the patients included in the study was 56.5±0.5 years (range= 29-82 years of age). The rates of abnormal and normal Pap tests were 12.1% (n=51) and 87.9% (n=372), respectively. Endometrioid adenocarcinoma was diagnosed in 82% (n=347) of the patients. The mean tumor diameter was calculated as 36.9±1.3mm (range= 1-150 mm). And, 77.1% (n=326) of the patients were in FIGO Stage 1, 48.9% (n=207) were in the low prognostic risk group. Clinico-pathological features of the study patients are given in Table 1.

The mean age was similar between the groups of patients with normal (56.3±0.5 years) and abnormal (58.1±1.5 years) Pap smear test (p= 0.198). In addition, tumor size, myometrial invasion, cervical involvement, LVSI, positivity of peritoneal cytology, involvement of lymph nodes and FIGO stage did not differ between the groups of normal and abnormal Pap test. Histology of non-endometrioid tumor type (p= 0.001), patients with adnexal involvement (p= 0.007) and the patients in the high prognostic risk group (p= 0.017) were found to be statistically significantly higher in the abnormal cervical cytology group. Pap test with malignant cells were detected mostly in non-endometrioid type tumors with a rate of 66.7%, and normal Pap test was detected mostly in endometrioid type tumors with a rate 90.5%. The rate of abnormal cytology was found to be 29.4% in the advanced and metastatic risk prognostic groups (Fig. 2). The results of all detailed analysis are given in Table 2.

Table 1. Clinico-pathological features and prognostic factors in patients who were surgically staged due to endometrial cancer (N= 423).

	N	%
Cytology		
Negative		
Normal	319	75.4
Inflamation	19	4.5
Infection	34	8.0
Positive		
ASC-US	18	4.3
ASC-H	4	0.9
HSIL	3	0.7
AGC, FN	13	3.2
AGC, NOS	1	0.2
AEC, NOS	5	1.2
Benign Endometrial Cells	4	0.9
Malignant Cells	3	0.7
Hystopathology Results		
Endometrioid Adenocarcinoma	347	82.0
Non-endometrioid Adenocarcinoma		
Serous Carcinoma	28	6.6
Carcinosarcom	15	3.6
Clear Cell Carcinoma	12	2.8
Mixt Carcinoma	9	2.1
Undifferentiated Carcinoma	7	1.7
Mucinous Carcinoma	5	1.2
MI		
< 50%	301	71.2

≥ 50%	122	28.8
Cervical Involvement		
No	368	87.0
Yes	55	13.0
Adnexal Involvement		
No	392	92.7
Yes	31	7.3
LVSI		
No	295	69.7
Yes	128	30.3
Peritoneal Cytology		
Negative	397	93.9
Positive	26	6.1
Lymph Node Involvement *		
Only Pelvic	18	
Only Paraaortic	3	
Pelvik and Paraaortic	19	
FIGO Stage		
I		
IA	264	62,4
IB	62	14,7
II	31	7,4
III		
IIIA	9	2,1
IIIB	4	0,9
IIIC1	15	3,5
IIIC2	18	4.3
IV		
IVA	3	0,7
IVB	17	4.0
Prognostic Risk Groups †		
Low	207	48.9
Intermediate	37	8.8
High-Intermediate	73	17.3
High	89	21.0
Advanced and metastatic	17	4.0

Abbreviation: N= Number, %= Percent, ASC-US= Atipical Squamous Cells-Undetermined Significance, ASC-H= Atipical Squamous Cells-Cannot Exclude High Grade Squamous Intraepithelial Lesions, HSIL= High-Grade Squamous Intraepithelial Lesion, AGC-FN= Atypical Glandular Cells - Favor Neoplasia, AGC-NOS= Atypical Glandular Cells – Not Other Specified, AEC-NOS= Atypical Endocervical Cells – Not Other Specified. MI= Myometrial Invasion, LVSI= Lymphovascular Space Invasion, * = Analysis was performed in 366 patients, † = The prognostic risk groups based on data from ESGO (European Society of Gynaecological Oncology) / ESTRO (European Society for Radiotherapy and Oncology) / ESP (European Society of Pathology) guideline for endometrial cancer (2020).

Table 2. Clinico-pathologic characteristics according to cervical cytology results (N= 423)

	Cervical Cytology		
	Negative (N= 372) n (%)	**Positive (N= 51) n (%)**	**P Value**
Age (mean years ± S.E)	56.3 ± 0.5	58.1 ± 1.5	0.198 ‡
Histopathology			**0.001**
Endometrioid	314 (90.5)	33 (9.5)	
Non-endometrioid	58 (76.3)	18 (23.7)	
Tumor Size (mean mm ± S.E)	37.5 ± 1.4	42.9 ± 4.3	0.188 ‡
MI			0.157
< 50 %	269 (89.4)	32 (10.6)	
≥ 50 %	103 (84.4)	19 (15.6)	
Cervical Involvement			0.052
No	328 (89.1)	40 (10.9)	
Yes	44 (80.0)	11 (20.0)	
Adnexal Involvement			**0.007** §
No	350 (89.3)	42 (10.7)	
Yes	22 (71.0)	9 (29.0)	
LVSI			0.070
No	265 (89.8)	30 (10.2)	
Yes	107 (83.6)	21 (16.4)	
Peritoneal Cytology			0.110 §
Negative	352 (88.7)	45 (11.3)	
Positive	20 (76.9)	6 (23.1)	
Lymph Node Involvement *			0.616
No	286 (87.5)	41 (12.5)	
Yes	33 (84.6)	6 (15.4)	
FIGO Stage			0.113 §
I	292 (89.6)	34 (10.4)	
II	25 (80.6)	6 (19.4)	
III	40 (87.0)	6 (13.0)	
IV	15 (75.0)	5 (25.0)	
Prognostic Risk Groups †			**0.017**
Low	192 (92.8)	15 (7.2)	
Intermediate	32 (84.2)	6 (15.8)	
High-Intermediate	63 (86.3)	10 (13.7)	
High	74 (83.1)	15 (16.9)	
Advanced and metastatic	12 (70.6)	5 (29.4)	

Abbreviation: N= Number, %= Percent, S.E= Standart Error, mm= Millimeter, MI= Myometrial Invasion, LVSI= Lymphovascular Space Invasion, * = Analysis was performed in 366 patients, † = The prognostic risk groups based on data from ESGO (European Society of Gynaecological Oncology) / ESTRO (European Society for Radiotherapy and Oncology) / ESP (European Society of Pathology) guideline for endometrial cancer (2020). Statistical analysis obtained by Pearson Chi-square test. ‡= based on Independent Samples T-Test. §= based on Fisher's Exact Test.

In the additional analysis of patients (n=347) whose pathology result was endometrioid type endometrial adenocarcinoma, factors other than FIGO grade did not differ between the normal and abnormal cytology groups. In patients with FIGO grades 1, 2 and 3 endometrioid type endometrial adenocarcinoma, abnormal cytology rates were calculated as 7.1%, 10.2%, and 22.9%, respectively (p= 0.014) (Fig. 3).

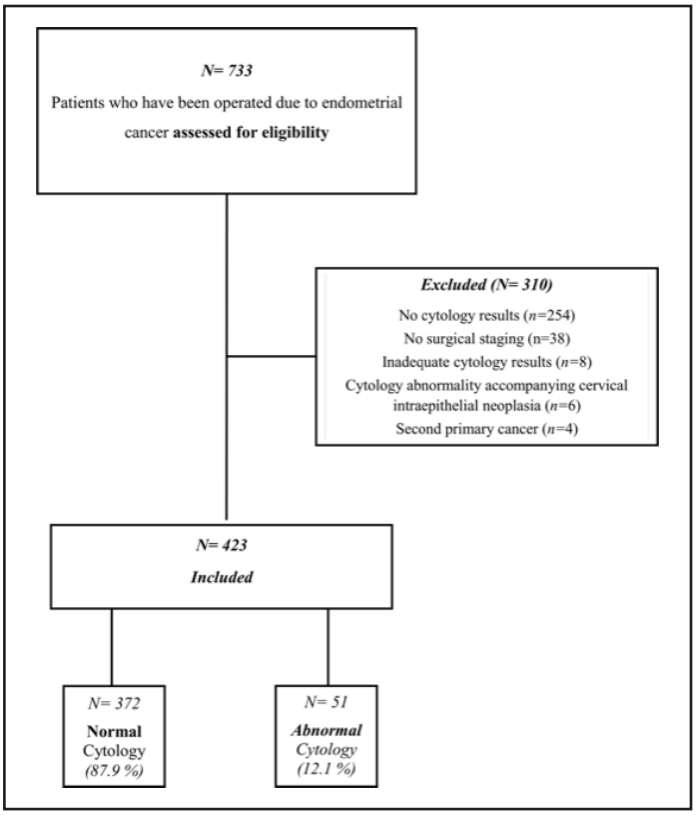

Figure 1. Flow diagram of the study.

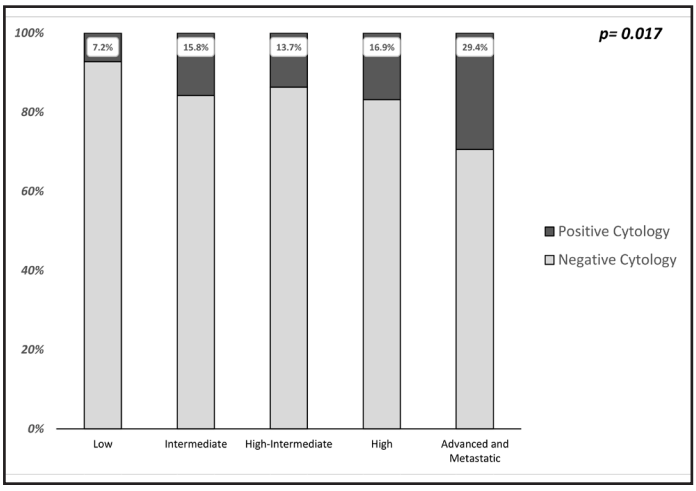

Figure 2. Percentage of positive cytology in prognostic risk groups.

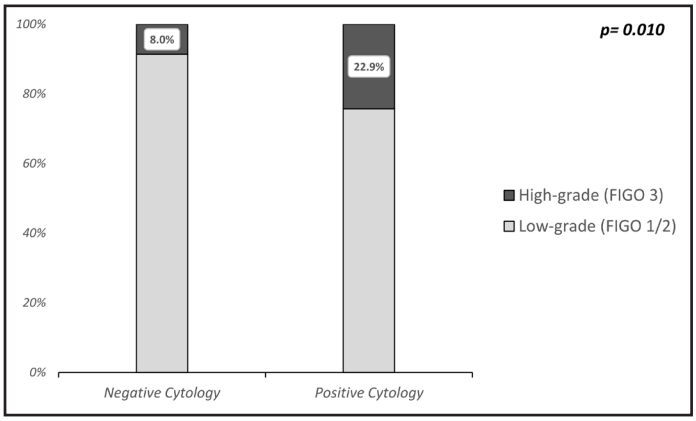

Figure 3. Percentage of high grade tumor according to negative and positive cytology groups.

DISCUSSION

Endometrial cancer is the most common gynecological cancer in the world and it's incidence has increased in recent years [6]. The intraoperative approach is total hysterectomy and bilateral salpingoopherectomy after the removal of the abdominal washing fluid. In order not to increase morbidity, surgical staging including lymph node dissection is performed in patients with high risk of lymph node involvement and debulking procedure is performed in patients with distant metastasis [7]. Therefore, surgical management is highly dependent on tumor histology and grade. However, preoperative and postoperative findings are generally inconsistent in high grade tumors [8]. Patient selection and prognostic factors have been the subject of research in many studies. It is thought that Pap smear test can contribute to the preoperative management and give an idea about the surgical approach [9,10]. So, we examined the relationship between preoperative Pap tests and clinico-pathological factors of patients with endometrial cancer. Our results independently suggested that Pap test abnormality may contribute to patient perioperative and postoperative management. According to analysis of the results of our data, preoperative abnormality of Pap tests were related with ESGO/ESTRO/ESP prognostic risk groups (molecular classification unknown). So, preoperative abnormality of Pap tests may predict the need of adjuvant treatment.

There is no accepted screening method for endometrial cancer. Although the rate of abnormal cytology in endometrial cancer in traditional Pap smear applications varies between 30-60%, it was reported as 45% in a recent large meta-analysis [2]. In our study, this rate was determined as 12%. Khumthong et al. [11] found that only 21% of 238 patients, 30% of whom had type 2

endometrial cancer, showed preoperative cytology abnormality, and this abnormality was an independent risk factor for cervical stromal invasion. In our study, a total of 12.1% cytological abnormalities were found in 423 patients, 18% of whom were non-endometrioid type tumors, and a borderline significance was found between cervical stromal involvement and smear abnormality. Mehta et al. [12] found preoperative abnormal cytology in 49% of 380 patients. Gu M et al. [13] evaluated 76 patients in their study, while abnormal Pap smear was associated with FIGO stage, they found no association with age, MI, and LVSI. In our study, we could not find relation between abnormal cytology results and FIGO stage. It has also been reported in the literature that abnormal pap smear tests require more staging and may be associated with more lymph node metastases [14,15]. On the contrary, there are studies reporting that Pap smear result will not affect this decision and it is not powerful in predicting lymph node metastasis [16]. In our study, lymph node involvement rates were not associated with abnormal Pap test.

Roelofsen et al. [9] found preoperative abnormal Pap test with a rate of 87.5% in patients with serous endometrial carcinoma and found the frequency of extra uterine disease to be significantly higher in this group. Similarly, abnormal results of Pap tests was found significantly more frequently in non-endometrioid type tumors in our study. We found the rate of abnormal cervical cytology to be 46.4% in patients with serous type carcinoma. This may be suggestive for the investigation of extra uterine metastases in the preoperative evaluation. This can be explained by the fact that non-endometrioid tumors are more brittle and shed easily.

Abu-Zaid et al. [17] evaluated only patients with endometrioid type endometrial adenocarcinoma and found preoperative abnormal cytology at a rate of 39% and showed that these abnormalities were not associated with FIGO stage, depth of MI, LVSI. In order to eliminate the bias that might be caused by analyzing endometrioid and non-endometrioid tumors in the same group, subgroup analysis was performed only in endometrioid type tumors. We found the rate of cytological abnormality as 9.5% in this group and increment of FIGO grade was positively correlated with increasing rate of abnormal cytology. The rate of abnormal cytology was found as 8% and 22.9% in low and high FIGO grade tumors, respectively. This may be due to the tendency of high-grade tumors to spill into vagina, as they are more aggressive and exhibit weaker cell connections.

The biggest shortcoming of our study is that it was retrospective and disease-free and overall survival rates could not be evaluated. It strengths are the inclusion of heterogeneous histological types and grades of tumors, the relatively large sample size, and the fact that it was performed in a single-center reference branch hospital. All pathology results were reported by expert gynecopathologists blinded to the diagnosis of endometrial cancer. Categorizing our patients according to prognostic risk groups gave us the opportunity to investigate the effect of Pap smear findings on prognosis. The histological classification of Endometrial Cancers of the World Health Organization and the International Society of Gynecological Pathology was updated in 2020 [18]. Again in 2020, an updated guideline for the diagnosis and treatment of patients with endometrial cancer was published by ESMO, ESGO and ESP associations. According to this guideline, prognostic risk groups are defined for cases where the molecular classification is known or unknown in the management of endometrial cancer, and adjuvant decision is applied according to these groups [4]. In our study, which was planned in this direction, we found that the rates of abnormal cervical cytology were significantly higher in non-endometrioid histology, high FIGO grade, adnexal involvement and high prognostic risk groups.

As a conclusion, we found that preoperative abnormal cervical cytology can predict the need for intraoperative systematic staging and postoperative adjuvant therapy in endometrial cancer.

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Original Research

Clinical, Laboratory and Radiological Evaluation of Intensive Care Patients Who Developed COVID-19 Associated Pneumomediastinum

Deniz Esin Tekcan Sanli[1], Elif Gulek[2], Neval Erozan[3], Serpil Kurtcan[4], Ibrahim Dikmen[2], Ahmet Necati Sanli[5], Ceyda Erel Kirisoglu[6], Duzgun Yildirim[3,7], Oner Dikensoy[8], Ibrahim Ozkan Akinci[2]

[1] Department of Radiology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[2] Department of Anesthesiology, Acibadem Kozyatagi Hospital, Istanbul, Turkey
[3] Department of Radiology, Acibadem Kozyatagi Hospital, Istanbul, Turkey
[4] Department of Radiology, Acibadem Taksim Hospital, Istanbul, Turkey
[5] Department of General Surgery, Abdulkadir Yüksel State Hospital, Gaziantep, Turkey
[6] Deparatment of Chest Diseases, Acibadem Kozyatagi Hospital, Istanbul, Turkey
[7] Department of Medical Imaging Techniques, Vocational School of Health, Acibadem University, Istanbul, Turkey
[8] Department of Anesthesiology, Acibadem Taksim Hospital, Istanbul, Turkey

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Correspondence
Deniz Esin Tekcan Sanli, MD
Address: Department of Radiology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
Email: tekcandenizesin@gmail.com

ABSTRACT

Objective: This study aims to identify possible risk factors and clinical, laboratory, or radiological predictors for COVID-19 associated pneumomediastinum.

Methods: Patients who developed pneumomediastinum under mechanical ventilation (MV) due to COVID-19 pneumonia during intensive care unit (ICU) (Group 1), and patients who died without developing pneumomediastinum during ICU (Group 2) were compared statistically in terms of age, laboratory parameters, medical treatments, mechanical ventilator parameters, and radiological findings.

Results: Group 1 patients were significantly younger than Group 2 patients ($p<0.05$). There was no significant difference between groups in terms of laboratory parameters except N/L ratios and sedimentation rates ($p>0.05$). There was no significant difference between the groups in terms of dominant infiltration pattern, pleural and pericardial effusion ($p>0.05$). The incidence of organizing pneumonia pattern, and infiltration of more than 75% of the total lung parenchyma were significantly higher in Group 1 ($p<0.01$). The rates of favipiravir treatment, immunomodulatory therapy and prone positioning were significantly lower in Group 1 than Group 2 ($p<0.01$). There was no significant difference between groups in terms of the duration of ICU hospitalization and MV, $PEEP_{max}$, PIP_{max} and PaO_2/FiO_2 ($p>0.05$).

Conclusion: Care should be taken in terms of pneumomediastinum in patients who show diffuse organized pneumonia patterns affecting more than 75% of the parenchyma area.

Keywords: COVID-19, pneumomediastinum, mortality, Computed Tomography

INTRODUCTION

It is known that SARS-CoV-2 virus, which has high infectivity rates, is asymptomatic or shows mild upper respiratory tract infection findings in most of the young and immunocompetent cases [1]. The virus infiltrating the lower respiratory tract, alarming the immune system and creating a cytokine storm may result in severe pneumonia [2]. Pulmonary involvement, which resolves within a few weeks without sequelae during the natural course of the disease in most of the cases, leads to more serious respiratory distress in immunosuppressive patients

and in the presence of comorbid disorders such as diabetes and hypertension [3,4]. In these patients, respiratory support may be required and even mechanical ventilator may be needed in the intensive care unit (ICU). It was noted that spontaneous pneumomediastinum (PM) developed in some cases in the course of COVID-19-related pneumonia, in some cases PM developed due to mechanical ventilation during intensive care treatment, and most of the patients who developed PM died in a short time [5,6]. Thereupon, a number of publications have been reported about PM, one of the most mortal complications of COVID-19 pneumonia; however, this situation has not yet been systematically evaluated [5,6]. In this study, we evaluated the patients who received respiratory support with a mechanical ventilator in the ICU and developed PM during the treatment together with their clinical, laboratory, medical and radiological features as a whole and compared with patients who did not developed PM during ICU. In this way, we aimed to give an idea to clinicians in terms of taking the necessary precautions in high-risk cases by determining possible risk factors or predictive parameters for PM.

MATERIALS AND METHODS

Study Population

SARS-CoV-2 PCR positive patients who were treated in the ICU of our hospital due to COVID-19 pneumonia between March 2020 and March 2021 and had a thorax computed tomography (CT) exam at the time of first admission to the hospital were included in the study to evaluate the radiological effect on PM objectively. The patients were divided into 2 groups; Group 1:Patients in ICU who developed PM at any stage of the disease, and Group 2:Patients who were treated in the ICU due to COVID-19 pneumonia and died, but never developed PM during the disease. The diagnosis of PM was made with the presence of subcutaneous emphysema in physical examination, X-Ray, and/or CT findings.

Main Points;

- Advanced age, male gender, and comorbid disease are not risk factors for the development of pneumomediastinum.
- The probability of pneumomediastinum is high in cases where the organizing pneumonia pattern diffusely affects more than 75% of the lung parenchyma area.
- Immunomodulatory and antiviral therapies may be preventive for the development of pneumomediastinum.
- Treating intensive care patients in prone position may prevent the development of pneumomediastinum.
- There is no direct relationship between increased intraalveolar pressure as a result of invasive mechanical ventilation and pneumomediastinum.

All Group 1 cases consisted of patients who developed PM while under invasive/noninvasive mechanical ventilator therapy. Spontaneous PM cases that developed during outpatient or inpatient treatment were excluded for Group 1 in order to evaluate the effect of mechanical ventilator on PM. Age, comorbid diseases, and mean durations of ICU hospitalization, durations of treatment with mechanical ventilator were recorded for both of groups. Also for Group 1, on which day of the mechanical ventilation PM developed was calculated (MV-PM interval).

Ethics committee approval was obtained for the study from the Acibadem University Clinical Research Ethics Committee (Date: 2021-03-10, Approbval Number: 2021-05/03).

Laboratory Parameters

Daily laboratory tests were performed on all patients for both groups. Laboratory parameters were taken into account before the development of PM in Group 1 patients and during all ICU hospitalizations in Group 2 patients. Laboratory parameters, including parameters predictive of severe disease or complications, hemoglobin (highest/lowest; Hb_{max}, Hb_{min}), platelet (highest/lowest, PLT_{max}, PLT_{min}), highest neutrophil (N_{max}), and the levels of leukocyte (Leu_{max}), lowest lymphocyte (L_{min}), highest neutrophil/lymphocyte ratio (N/L_{max}), $D\text{-}Dimer_{max}$, LDH_{max}, $Procalcitonin_{max}$, $Ferritin_{max}$, $Fibrinogen_{max}$, $IL\text{-}6_{max}$, CRP_{max} accounts and erythrocyte sedimentation rate (ESR_{max}) were evaluated. In addition, secondary viral, bacterial and/or fungal infection during the ICU of the patients and isolated agents were recorded.

Radiological Evaluation-CT Imaging Method and Image Analysis

All cases had tomographic exams since the patients who had at least one thorax CT exam at the time of first admission before they were taken to the ICU were included in the study. Patients with CT images were selected for the study in order to make an optimal assessment of the predictivity of radiological parameters on PM. Since ground-glass opacities (GGOs), crazy-paving patterns, low level of pleural-pericardial effusion are not usually seen on X-Ray.In patients with multiple CT scans, the most progressive CT imaging features obtained at the time of

development of PM for Group 1 and the most progressive of all CTs in Group 2 were evaluated. Radiologic evaluations after admission to the ICU were made with portable radiographies. However, radiography features were not evaluated in the study. All CT scans were done with Siemens Somatom Sensation-Syngo CT 2009 device using a low-dose noncontrast CT protocol. The acquisition parameters were standardized as: tube voltage, 140 kV; tube current, 40 mA; pitch, 1.4; FOV, 455 mm; slice thickness, 64×0.6 mm. Images were converted into 1 mm thin reconstructions in the lung parenchyma window.

All images were evaluated separately by two radiologists with approximately 25 years (D.Y.) and 10 years (D.E.T.S) of practical experience in chest CT. Radiologically typical/atypical presentations of cases were evaluated according to the criteria of the Radiological Society of North America (RSNA) Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19, as of April 2020 [7].

CT imaging features were evaluated according to the RSNA guideline, as are typical/atypical imaging features for COVID-19 pneumonia, the presence of organized pneumonia, presence of unilateral/bilateral involvement, dominant infiltration pattern (ground-glass opacities, crazy-paving, consolidation), the distribution of GGOs, crazy-paving, and consolidation patterns were classified as peripheral (distal 1/3 of lung parenchyma), central and diffuse, while lobar distribution pattern of infiltrates (lower lobes-upper lobes-widespread) [7,8]. The percentage of infiltrating total lung parenchyma (1, <25%; 2, 25%–50%; 3, 50%–75%; 4, >75%) were also calculated in multiplanar images [7,9]. The affected lung areas were measured electronically in continuous reconstructed axial sections 10 mm section thickness, then the sum of the sequential areas was recorded. These measurements were all achieved by MPR images with Syngo.Via Software (VB10B, Siemens). In atypical or suspicious cases, CT images were reevaluated together and a consensus was reached.

Although the diagnosis of PM was made clinically in patients who developed PM, it was also proven radiologically. In other words, CT images were taken even after PM developed in Group 1 patients.

Medical Treatment and Mechanical Ventilator Pressures

Patients were evaluated according to which SARS-CoV-2 targeted drugs they took during their treatment (hydroxychloroquine, azithromycin, favipiravir) and whether they received immunomodulatory treatment (glucocorticoid, anti-cytokine drugs). The mechanical ventilator (MV) pressure parameters ($PEEP_{max}$, PIP_{max}) ve PaO2/FiO2 were recorded. In addition, the prone position application status of the patients was evaluated.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. Student-t test was used for comparisons between two groups of normally distributed quantitative variables, and Mann-Whitney U test was used for comparisons between two groups of non-normally distributed quantitative variables. Pearson chi-square test, Fisher's exact test and Fisher-Freeman-Halton test were used to compare qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

A total of 38 patients were included in the study; 16 patients in Group 1, and 22 in Group 2. The mean age of the patients was 61,79±15,49 (16-95) and it was significantly lower in Group 1 (Group 1 mean age: 53.94±14.87; Group 2 mean age 67.50±13.55) (p=0.006) (Table 1). Although the number of male patients was higher than females in both groups, There was no significant difference between the groups in terms of gender and presence of additional disease (p=0.310, p=0.290, respectively) (Table 1). PM developed while all Group 1 patients were under mechanical ventilator therapy in the ICU.

The mean interval between the first admission to the ICU and the development of PM of Group 1 patients was 19.81±9.42 (9-35) days. The mean interval from MV to developing PM was 13.68±10.73 (1-30) days in Group 1 patients. The mean duration of ICU hospitalization of Group 1 patients was 29.1±9.6 (12-46) days, while that of Group 2 patients was 37.8±30.7 (1-150). While the mean duration of MV in Group 1 patients was 23±11.4 (5-40) days, it was 35.4±29 (1-140) days in Group 2 patients. There was no statistically significant difference between the groups in terms of the duration of ICU hospitalization and mechanical ventilation (p=0.293; p=0.124, respectively) (Table 1). Only 3 of Group 1 patients was discharged; 13 patients died (mortality rate 81.25%).

Table 1. Clinical and Laboratory Results by Presence of Pneumomediastinum

Total (n=38)		Pneumomediastinum			
		Yes (n=16)	No (n=22)	p	
Age	*Min-Max (Median)*	16-95 (59.5)	16-74 (57.5)	41-95 (69.5)	[a]***0.006***
	Mean±SD	61.79±15.49	53.94±14.87	67.50±13.55	
Gender	*Female*	28 (74)	12 (75)	16 (73)	[b]***0.310***
	Male	10 (26)	4 (25)	6 (27)	
Comorbidity	*No*	13 (34.2)	7 (43.8)	6 (27.3)	[b]***0.290***
	Yes	25 (65.8)	9 (56.3)	16 (72.7)	
Hospitalization in the ICU (day)	*Min-Max (Median)*	1-150 (28)	12-46 (27.5)	1-150 (30)	[a]*0.293*
	Mean±SD	34.2±24.5	29.1±9.6	37.8±30.7	
Mechanical ventilation (day)	*Min-Max (Median)*	1-140 (22)	5-40 (21)	1-140 (27.5)	[a]*0.124*
	Mean±SD	30.2±24	23±11.4	35.4±29	
Hemoglobin *(g/dL)*	*Min-Max (Median)*	8.6-13.5 (11.1)	9.2-12.7 (11.2)	8.6-13.5 (11.1)	[a]***0.798***
	Mean±SD	11.15±1.23	11.09±1.23	11.19±1.26	
Leukocyte *(uL)*	*Min-Max (Median)*	3400-72250 (19425)	3400-31700 (17635)	9000-72250 (19480)	[c]***0.231***
	Mean±SD	21545.53±11709.25	18270±7716.37	23927.73±13598.48	
Neutrophil *(uL)*	*Min-Max (Median)*	1300-55600 (17700)	1300-27700 (17300)	7670-55600 (17700)	[a]***0.186***
	Mean±SD	18400±9898.83	15886.88±7981.67	20227.73±10900.77	
Lymphocyte *(uL)*	*Min-Max (Median)*	150-3000 (465)	150-3000 (615)	150-840 (425)	[c]***0.308***
	Mean±SD	592.37±520	773.13±745.45	460.91±191.04	
N/L	*Min-Max (Median)*	1.4-161.3 (28.1)	4-161.3 (19.5)	1.4-152.7 (39.8)	[c]***0.017****
	Mean±SD	44.76±42.23	33.00±41.44	53.31±41.64	
Platelets *(×10³ /uL)*	*Min-Max (Median)*	90-447.5 (252.3)	90-391.5 (244.3)	116.5-447.5 (263)	[a]***0.242***
	Mean±SD	255.24±89.61	235.06±82.32	269.91±93.66	
IL-6 *(pg/mL)*	*Min-Max (Median)*	2-290 (54)	5.6-177 (48.9)	2-290 (68.4)	[c]***0.301***
	Mean±SD	75.11±76.34	51.32±39.23	92.42±91.78	
CRP*(mg/dL)*	*Min-Max (Median)*	1.2-59.3 (24.9)	1.2-58.7 (21.6)	9.1-59.3 (26.4)	[a]***0.214***
	Mean±SD	23.99±13.27	20.82±14.8	26.3±11.86	
ESR *(mm/h)*	*Min-Max (Median)*	4-150 (58.5)	56-150 (92.5)	4-67 (31)	[a]***0.001****
	Mean±SD	59.55±34.86	91.88±25.06	36.05±17.84	
D-dimer *(µg/mL)*	*Min-Max (Median)*	0.5-15.4 (4)	1.5-12 (5)	0.5-15.4 (2.6)	[c]***0.174***
	Mean±SD	4.75±3.72	5.45±3.27	4.24±4.01	
LDH *(IU/L)*	*Min-Max (Median)*	50-1638 (397)	185-1638 (382)	50-1076 (416.5)	[c]***0.679***
	Mean±SD	481.11±290.68	481.19±332.61	481.05±264.29	
Ferritin *(ng/mL)*	*Min-Max (Median)*	123-16500 (1518.5)	129-16500 (1582.5)	123-8853 (1482)	[c]***0.615***
	Mean±SD	1958.24±2914.39	2499.38±3980.24	1564.68±1806.58	
Fibrinogen *(mg/dL)*	*Min-Max (Median)*	118-900 (485)	411-900 (631)	118-804 (305)	[a]***0.001****
	Mean±SD	495.34±222.38	627.25±161.2	399.41±213.71	

Procalcitonin *(ng/mL)*	*Min-Max (Median)*	0.01-108 (2.42)	0.1-75.5 (1.55)	0.01-108 (3.4)	***[c]0.139***
	Mean±SD	9.80±21.32	7.02±18.53	11.82±23.34	
Secondary Infection	*No*	17 (44.7)	12 (75.0)	5 (22.7)	***[b]0.001*****
	Yes	21 (55.3)	4 (25.0)	17 (77.3)	
Favipravir	*No*	12 (31.6)	10 (62.5)	2 (9.1)	***[b]0.001*****
	Yes	26 (68.4)	6 (37.5)	20 (90.9)	
Immune Modulatory Therapy	*No*	20 (52.6)	12 (75.0)	8 (36.4)	***[b]0.019****
	Yes	18 (47.4)	4 (25.0)	14 (63.6)	
Prone Positioning	*Yes*	19 (50.0)	13 (81.3)	6 (27.3)	***[b]0.001*****
	No	19 (50.0)	3 (18.8)	16 (72.7)	
$PEEP_{max}$ *(cm H2O)*	*Min-Max (Median)*	8-16 (12)	10-14 (12)	8-16 (12)	***[a]0.813***
	Mean±SD	11.53±2.15	11.63±1.67	11.45±2.48	
PIP_{max} *(cm H2O)*	*Min-Max (Median)*	15-45 (40)	30-45 (40)	15-45 (37.5)	***[c]0.099***
	Mean±SD	37.16±6.67	39.5±4.08	35.45±7.7	
PaO_2/FiO_2	*Min-Max (Median)*	40-130 (60)	50-80 (59)	40-130 (65)	***[c]0.094***
	Mean±SD	65.34±19.42	58.5±9.56	70.32±23.19	

N/L, neutrophil to lymphocyte ratio; CRP, C-reactive protein;ESR, Erythrocyte Sedimentation Rate; LDH, Lactate dehydrogenase; PEEP, Positive end-expiratory pressure;PIP, Peak inspiratory pressure, PaO2/FiO2, Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration; [a]Student-t Test, [b]PearsonChi-Square Test, [c]Mann Whitney U Test **p<0.01

Laboratory Parameters

In the evaluation of laboratory parameters, there was no statistically significant difference in $Hb_{min-max}$, Leu_{max}, N_{max}, L_{min}, , PLT_{max}, PLT_{min}, IL-6_{max}, CRP_{max}, D-$dimer_{max}$, LDH_{max}, $Ferritin_{max}$, $Procalsitonin_{max}$measurements between the groups (p>0.05) (Table 1). ESR_{max} and $Fibrinogen_{max}$ levels were found to be significantly higher in Group 1 (p= 0.001, p= 0.001; p<0.01). Secondary infection incidence and N/L_{max} ratios were lower in Group 1 than Group 2 (p=0.001, p=0.017; p<0.01, respectively). Secondary infectious agents included CMV, Candida sp., Staphylococcus sp., Klebsiella, Pseudomonas, Pneumocystis jirovecii, Enterobacter sp., and the most frequently isolated agent was Candida (Table 2).

Radiological Evaluation

All of Group 1 cases; 86.4% of Group 2 cases showed typical imaging findings, but no significant difference was found between the groups (p>0.05). The incidence of organizing pneumonia pattern, involvement of more than 75% of the lung parenchyma, and detection of diffuse distribution pattern were significantly higher in Group 1 (p=0.001, p<0.01) (Figure 1a,b,c). While organizing pneumonia pattern was observed in 87.5% of Group 1 cases; organizing pneumonia pattern was detected in only 22.7% of Group 2 cases (Figure 2a,b). According to the groups, no statistically significant difference was found in terms of unilateral/bilateral involvement of the cases, dominant infiltration pattern, dominant lobar distribution (upper lobe/ lower lobe), presence of pleural and pericardial effusion (p>0.05) (Table 3) (Figure 3,4,5).

Medical Treatment and Mechanical Ventilator Parameters

The rate of favipravir treatment, immune modulator treatment and prone position application in Group 1 cases was found to be statistically significantly lower than Group 2 (p=0.001; p=0.019; p=0.001, p<0.05). In addition, none of the Group 1 patients were treated with hydroxychloroquine and azithromycin.There was no significant difference between the groups in terms of $PEEP_{max}$, PIP_{max}, PaO2/Fio2 ratios (p>0.05) (Table 1).

The MV parameter values, comorbid diseases of the patients, which treatments were applied, and which infectious agents were produced are given in Table 2 in detail.

Table 2. Characteristics of patients in the ICU with and without pneumomediastinum

		Age	Hospitalization in the ICU (day)	ICU admission to PM interval (day)	IMV-PM interval (day)	Duration of IMV	Comorbidity	Treatment (Favipiravir)	Secondary infection	$PEEP_{max}$ ($cm H_2O$)	PIP_{max} ($cm H_2O$)	Min PaO_2/FiO_2	Immune Modulatory Therapy	Prone Position
Pneumomediastinum (+)	Case 1	60	25	10	7	22	-	-	-	12	40	50	-	-
	Case 2	59	12 (Alive)	9	2	5	-	Favipiravir	*CMV, Candida Albicans, Staphylococcus spp.*	10	40	58	pulse steroid (2x250mg 250 mg prednisone, 3 days)	-
	Case 3	74	40	30	25	35	HT	Favipiravir	*Stenotrophomonas Maltophilia, CMV, Candida Albicans*	10	35	50	pulse steroid (2x250mg 250 mg prednisone, 3 days)	-
	Case 4	44	15	9	5	11	-	Favipiravir	-	10	30	60	-	-
	Case 5	56	26	16	10	20	DM	-	-	14	45	60	-	-
	Case 6	58	23	10	9	22	-	-	-	12	40	58	-	-
	Case 7	71	37	26	26	37	HT	Favipiravir	*CMV, Candida Albicans, Pneumocystis carinii*	12	45	50	pulse steroid (2x250mg 250 mg prednisone, 3 days)	+
	Case 8	40	40	30	26	36	-	-	-	10	40	50	-	-
	Case 9	63	30	25	23	28	Lung CA	-	-	10	40	60	-	-
	Case 10	55	21	10	9	20	-	Favipiravir	-	10	35	60	-	-
	Case 11	54	40	30	30	40	HT, DM	-	-	12	40	60	-	-
	Case 12	31	46	35	29	40	-	-	-	14	45	50	-	-
	Case 13	16	36	30	10	16	Immunodeficiency	-	-	12	40	80	-	-
	Case 14	58	28	20	6	14	DM, Emphysema	-	-	14	42	100	-	-
	Case 15	57	20 (Alive)	15	1	6	DM	Favipiravir	-	10	40	120	-	+
	Case 16	67	27	12	1	16	Emphysema	-	*Stenotrophomonas Maltophilia, Pseudomonas Aeruginosa, Acinetobacter Baumannii, Staphylococcus spp.*	14	35	50	2x40mg prednisone	+
Pneumomediastinum (-)	Case 1	80	20			18	HT	Favipiravir	*Escherichia coli, Stenotrophomonas Maltophilia*	12	40	69	2x40mg prednisone	+
	Case 2	95	10			10	HT, DM	Favipiravir, Azithromyci, Hydroxychloroquine)	*Candida Albicans*	10	35	100	2x40mg prednisone	-
	Case 3	85	1			1		-	-	8	30	80		-
	Case 4	80	16			14	HT, DM, IHD, CeVD	-	*Klebsiella Pneumoniae, Candida spp., Staphylococcus spp.*	12	45	80	2x40mg prednisone	-
	Case 5	62	21			20	HT, DM	Favipiravir	-	8	40	130	2x40mg prednisone	-

Pneumomediastinum (-)	Case 6	54	19			15	İKH, HT	Favipiravir	*Acinetobacter Baumannii, Klebsiella Pneumoniae, Candida Albicans*	14	15	58	2x40mg prednisone	+
	Case 7	70	45			40	DM, HT, CeVD	Favipiravir	*Acinetobacter Baumannii, Klebsiella Pneumoniae, CMV*	10	25	65	2x40mg prednisone	+
	Case 8	60	18			18	HT, DM	Favipiravir	*Klebsiella Pneumoniae, Candida Albicans*	14	40	48	2x40mg prednisone	+
	Case 9	56	37			35	-	Favipiravir	*Stenotrophomonas Maltophilia, Staphylococcus spp.*	14	40	40	Anakinra, pulse steroid (2x250mg 250 mg prednisone, 3 days)	+
	Case 10	58	16			15	-	Favipiravir	*Candida Albicans*	12	35	55	2x40mg prednisone	+
	Case 11	69	38			35	COPD, HT, DM	Favipiravir	*Candida spp., Escherichia coli, Staphylococcus spp.*	12	30	65	2x40mg prednisone	+
	Case 12	75	60			58	HT, DM, OSAS	Favipiravir, Azithromyci, Hydroxychloroquine)	*Candida Albicans*	14	30	60	-	+
	Case 13	78	28			25	Atrial fibrillation	Favipiravir, Azithromyci, Hydroxychloroquine)	-	10	30	80	-	-
	Case 14	41	47			46	-	Favipiravir, Azithromyci, Hydroxychloroquine)	-	10	40	94	-	+
	Case 15	73	80			75	COPD, HT, İKH	Favipiravir	*Candida Albicans, Pseudomonas Aeruginosa*	8	45	50	-	+
	Case 16	70	53			52	HT,DM	Favipiravir, Azithromyci, Hydroxychloroquine)	*Candida Albicans*	14	45	69	2x40mg prednisone	+
	Case 17	55	32			31	Hyperlipidemia, Hypothyroidism	Favipiravir, Azithromyci, Hydroxychloroquine)	*Candida Albicans*	16	30	61	2x40mg prednisone	+
	Case 18	53	150			140	-	Favipiravir, Azithromyci, Hydroxychloroquine)	-	12	30	68	2x40mg prednisone	+
	Case 19	51	60			58	-	Favipiravir, Azithromyci, Hydroxychloroquine)	*Enterobacter cloacae*	14	40	50	-	+
	Case 20	77	25			22	Emphysema, COPD	Favipiravir, Azithromyci, Hydroxychloroquine)	*Klebsiella Pneumoniae*	8	45	55	-	+
	Case 21	59	33			30	DM	Favipiravir	*Staphylococcus spp., Candida spp.*	12	40	50	-	+
	Case 22	84	23			20	HT, DM, Parkinson	Favipiravir	*Acinetobacter Baumannii, Staphylococcus spp., Candida spp.*	8	30	120	Tocilizumab	-

ICU, Intensive care unit; IMV, Invasive mechanical ventilation; PM, pneumomediastinum; HT, Hypertension; DM, Diabetes Mellitus; CA, Cancer, IHD, Ischemic heart disease; PEEP, Positive end-expiratory pressure;PIP, Peak inspiratory pressure; CeVD, Cerebrovascular disease; OSAS, obstructive sleep apnea syndrome; COPD, Chronic obstructive pulmonary disease

Table 3. Radiological Findings by Presence of Pneumomediastinum

		Pneumomediastinum			
		Total (n=38)	Yes (n=16)	No (n=22)	p
		n (%)	n (%)	n (%)	
CT findings	**Typical**	35 (92.1)	16 (100.0)	19 (86.4)	[d]***0.249***
	atypical	3 (7.9)	0 (0.0)	3 (13.6)	
Organized pneumonia	**No**	19 (50.0)	2 (12.5)	17 (77.3)	[b]***0.001****
	Yes	19 (50.0)	14 (87.5)	5 (22.7)	
Percentage of Parenchymal Involvement	**1**	16 (42.1)	2 (12.5)	14 (63.6)	[e]***0.001****
	2	8 (21.1)	1 (6.3)	7 (31.8)	
	3	2 (5.3)	2 (12.5)	0 (0.0)	
	4	12 (31.6)	11 (68.8)	1 (4.5)	
Laterality	**Uniateral**	4 (10.5)	0 (0.0)	4 (18.2)	[d]***0.124***
	Bilateral	34 (89.5)	16 (100.0)	18 (81.8)	
Dominant infiltration pattern	**Ground-glass opacity**	20 (52.6)	7 (43.8)	13 (59.1)	[e]***0.402***
	Crazy-paving	14 (36.8)	8 (50.0)	6 (27.3)	
	Consolidation	4 (10.5)	1 (6.3)	3 (13.6)	
Dominant lobar distrubition	**Upper lobes**	7 (18.4)	1 (6.3)	6 (27.3)	[e]***0.053***
	Lower lobes	7 (18.4)	1 (6.3)	6 (27.3)	
	Diffuse	24 (63.2)	14 (87.5)	10 (45.5)	
Distribution	**Basal**	18 (47.4)	3 (18.8)	15 (68.2)	[e]***0.001****
	Central	3 (7.9)	0 (0.0)	3 (13.6)	
	Diffuse	17 (44.7)	13 (81.3)	4 (18.2)	
Pleural Effusion	**No**	26 (68.4)	10 (62.5)	16 (72.7)	[b]***0.503***
	Yes	12 (31.6)	6 (37.5)	6 (27.3)	
Pericardial Effusion	**No**	35 (92.1)	13 (81.3)	22 (100.0)	[d]***0.066***
	Yes	3 (7.9)	3 (18.8)	0 (0.0)	

CT, Computed tomography; [b]PearsonChi-Square Test [d]Fisher's Exact Test [e]Fisher Freeman Halton Test **p<0.01

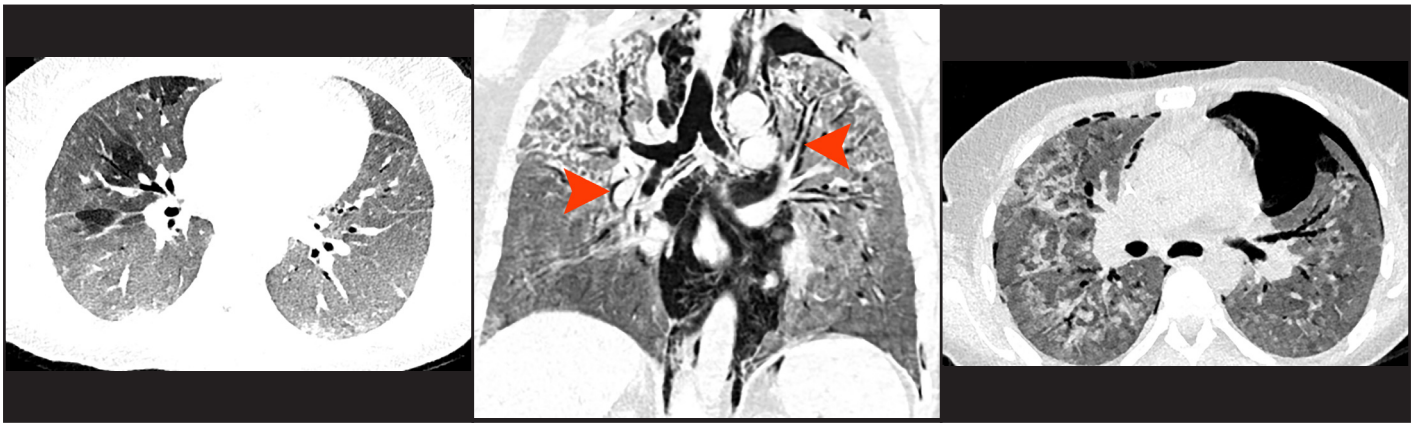

Figure 1. A 44-year-old female patient who developed pneumomediastinum and died while under mechanical ventilation support secondary to COVID-19 pneumonia. a; On thorax CT, it is seen that more than 75% of the lung parenchyma area is infiltrated. 1b; Pneumomediastinum developed on the 44th day during ICU hospitalization. Note that almost all lung parenchyma areas are infiltrated and perivascular free air images (red arrowhead). c; On the second control thorax CT obtained ten days later, it is seen that the pneumomediastinum still continues but is concentrated in the left hemithorax.

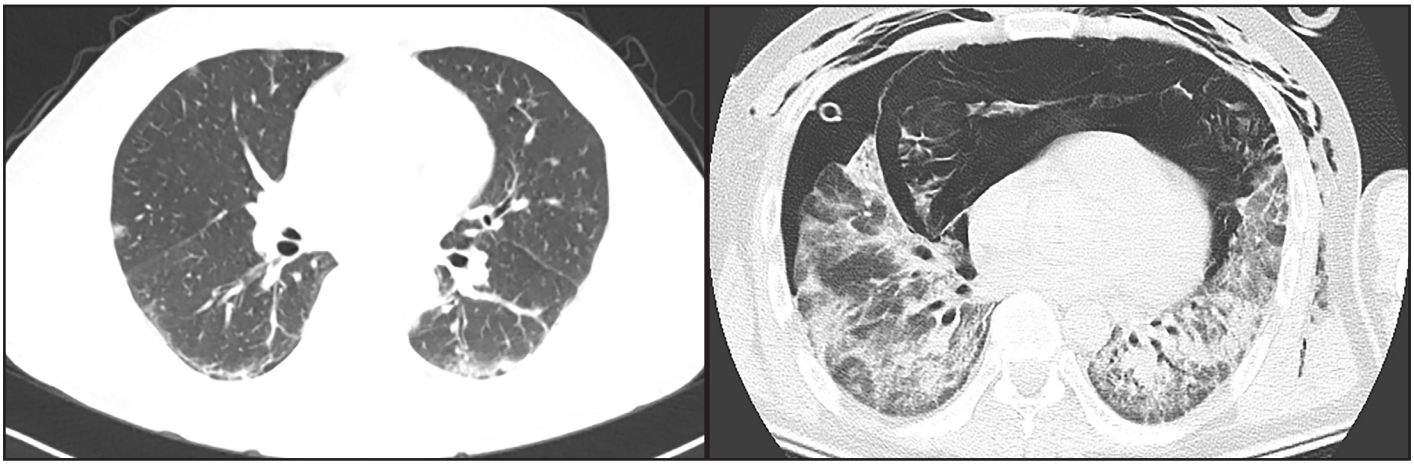

Figure 2. SARS-CoV-2 PCR(+), 40-year-old male patient,**a:** In the thorax CT examination taken at the first admission to outpatient on 25.10.2020, minimal infiltration is seen in the ground glass density, which shows a typical peripherobasal location for COVID-19 pneumonia in the bilateral lower and upper lobes of the lung. 10 days after this exam, the patient was taken to the intensive care unit due to the rapid deterioration of the clinical condition and the need for respiratory support. **b:** Extensive pneumomediastinum and subcutaneous emphysema are seen on thoracic CT in the patient under treatment in the ICU. The patient died 18 days after this exam.

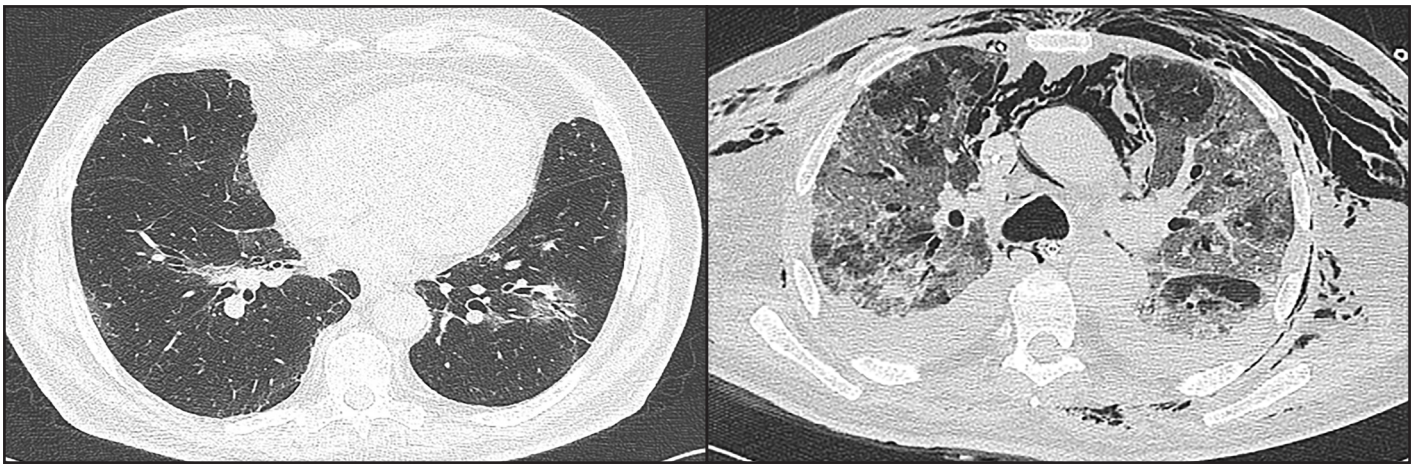

Figure 3. A 70-year-old male patient who developed pneumomediastinum and died due to COVID-19 pneumonia under mechanical ventilation in the ICU. **a:** Ground-glass opacities and minimal infiltration in crazy-paving pattern are seen in the lung parenchyma areas in thorax CT taken during outpatient admission dated 09.01.2021. **b:** On the thorax CT performed while under treatment in the ICU, 1 month after this exam, it is seen that infiltration, pneumomediastinum and subcutaneous emphysema develop an organized pneumonia pattern in which the lung parenchyma areas are almost completely affected. Note the bilateral pleural effusion.

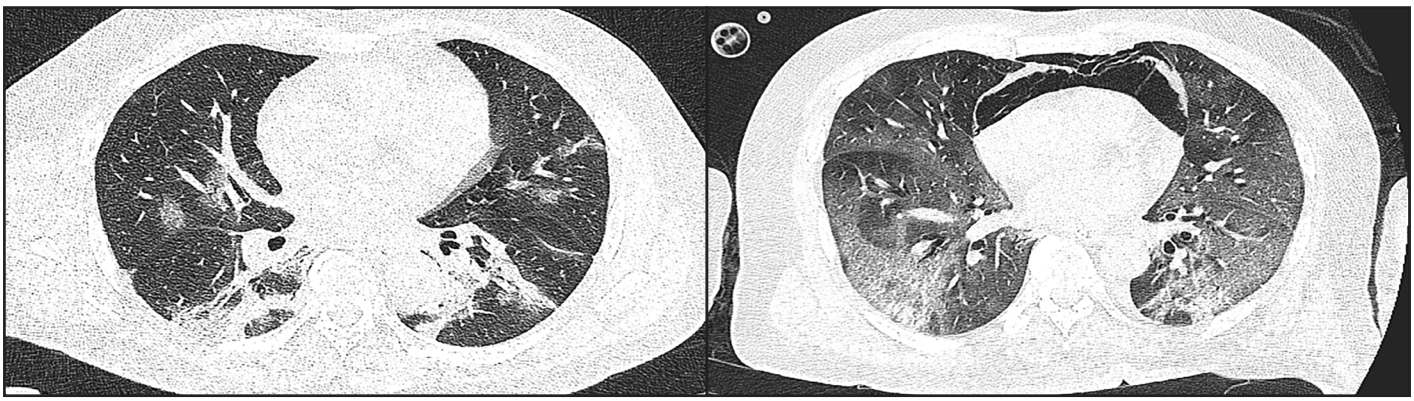

Figure 4. A 48-year-old male patient who developed pneumomediastinum during ICU hospitalization but was discharged without sequelae. **a:** Focal consolidations and minimal infiltrations in crazy-paving pattern are observed in thorax CT dated 13.04.2021. **b:** Minimal pneumomediastinum is seen on thorax CT taken under mechanical ventilation support in the ICU 6 days after this examination.

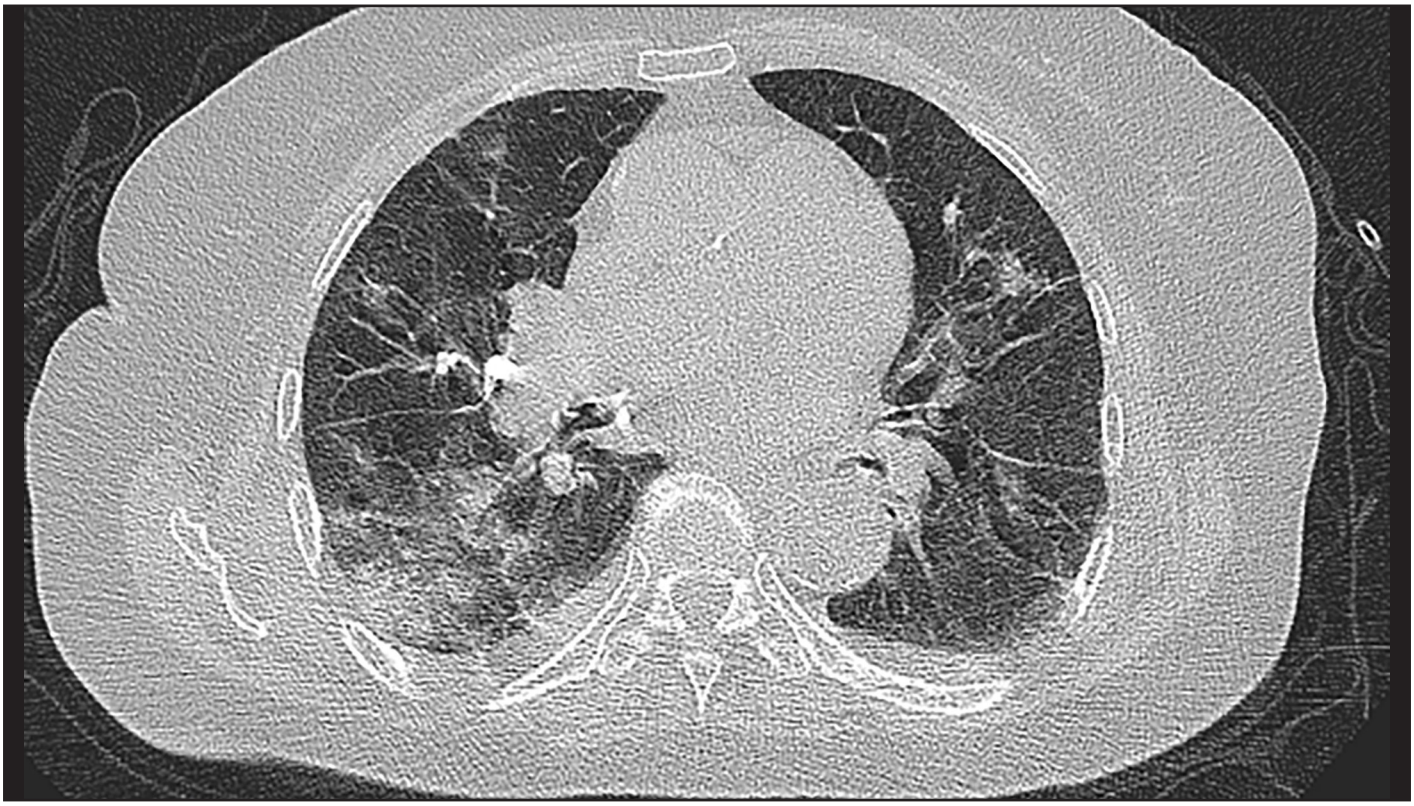

Figure 5. A 69-year-old female patient who stayed in the ICU for 38 days and received respiratory support for 35 days, but did not develop pneumomediastinum during her treatment, shows bilateral minimal pleural effusion and ground-glass parenchymal infiltrates on the thorax CT image. The patient died not because of respiratory failure, but because of secondary infections.

DISCUSSION

Although the mortality of COVID-19-associated pneumonia differeces in distinct countries, it is generally quite high compared to other infective agents [10]. Clinical outcomes of pneumonia due to COVID-19 is more severe in elderly, immunosuppressive, comorbid male patients who had secondary bacterial infection during COVID-19 [3,4,11]. Most of these patients need a short or long term mechanical ventilator during the course of the disease. It has been reported that mortality rates are higher in patients need mechanical ventilation support [3]. The timing of starting mechanical ventilation and duration is also important at this stage [12]. It has come to our attention that PM, which has a very mortal course, can develop in a small part of these patients under mechanical ventilator treatment. Although a definite reason has not been revealed yet, the most accepted thought is as the fragility of the alveolar mucosa as a result of the widespread damage caused by the virus in the alveoli, and the rupture of the alveoli by increasing the intraalveolar pressure with mechanical ventilation. This situations results with spreading the air to the mediastinum and subcutaneously along the perivascular spaces (Figure 1b, 3b) [5,13,14]. In other words, PM is the presence of air images in the intrathoracic and subcutaneous fatty planes caused by rupture of fragile airways with barotrauma (Figure 1c, 2b, 3b, 4b) [6]. While the rate of PM development due to MV in ARDS cases is around 6.5%; McGuinness et al. showed that patients with COVID-19 patients are more prone to barotrauma due to MV compared to ARDS cases developing secondary to other causes (Figure 1) [15,16]. Advanced PM produces an enormously increased intrathoracic pressure [17]. The major cause of mortality due to PM is explained as increased intrathoracic pressure leading to cardiac failure due to vascular return failure [17]. Most of the cases die as a result of cardiopulmonary arrest caused by increased intrathoracic pressure (Figure 1b,2b) [17]. However, while PM does not develop in the majority of cases treated with higher pressures, it is still a mystery that some patients develop PM even at low pressures. In this study, it was aimed to shed light on clinicians in the treatment process by determining possible risk factors or some predictive parameters for PM. According to the results of the study, It has been shown that male gender, advanced age, history of comorbid disease and the development of secondary infection during COVID-19 pneumonia, which

are accepted as risk factors for severe disease, are not a marker for PM. In fact, patients who developed PM were significantly younger than those who did not. When laboratory parameters were evaluated, it was shown that parameters such as D-Dimer, LDH, IL-6, CRP, and procalcitonin, which have prognostic value in severe disease, were not important for the prediction of PM [18,19].

When evaluated in terms of radiological parameters; it has been shown that cases with widespread involvement of the upper lobes in the form of crazy-paving and consolidation during COVID-19 pneumonia require more intensive care support [9]. Similarly, most of our cases showed these features radiologically, and all of them needed intensive care. However, diffuse infiltration of more than 75% of the total lung parenchyma area, including the central portions, especially in the organizing pneumonia pattern, was significantly higher in the PM group. Organized pneumonia is defined as the radiological appearance of exudate that occurs catastrophically with the inclusion of chronic inflammatory cells in the alveolar inflammation, mostly in the subacute-late period of the disease [20]. Alveolar epithelial cells become more fragile under this intense inflammation. For this reason, when exposed to high intraalveolar pressure such as the valsalva maneuver or mechanical ventilation, they are damaged immediately and patients enter hypoxemia very quickly [20,21]. As the result, the ventilation balance will be disturbed and the clinical picture results in acute respiratory distress syndrome (ARDS) [21]. Corticosteroid therapy, which is started in these patients in the early period, is often life-saving by suppressing inflammatory cells [20,21]. In our study, the presence of typical/atypical imaging findings in terms of COVID-19, ground glass opacities/crazy-paving/consolidation infiltration pattern, upper-lobe involvement, pleural-pericardial effusion did not differ significantly in terms of development of PM.

Many medical treatments such as chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir, remdesivir, and ivermectin have been tried against the SARS-CoV-2 viral agent since the early period of the pandemic [10]. However, it has been shown that favipiravir treatment provides faster clinical improvement by rapid viral clearance, therefore, it is more effective than other drugs and can be used safely in the treatment of COVID-19 [22]. In our study, the rates of receiving favipiravir treatment were significantly lower in patients who developed PM. Perhaps, if favipiravir had been started in these patients in the early stages of the disease, the virus would have been controlled easily and quickly. So that ARDS would not have occurred and PM would not have been developed since it would not have exacerbated the systemic and alveolar inflammatory response too much. Again, immunomodulatory treatments such as tocilizumab and IL antagonists, especially corticosteroids, have been used extensively in the treatment of COVID-19 to suppress cytokine release and complications caused by cytokine storms [23,24]. In our study, the use of immunomodulatory therapy was significantly lower in the PM group. We think that this situation may increase cytokine-dependent alveolar damage and pave the way for PM.

We mentioned that the main mechanism responsible for the development of COVID-19-associated PM is barotrauma caused by mechanical ventilation on the basis of alveolar damage. Mortality rates increase in intubated COVID-19 patients with or without PM [25]. Therefore, patient selection for intubation is critical [25]. Intubation time is also important, and early respiratory therapy in critically ill patients increases surveillance [26]. However, in cases where the cytokine storm is heavy, one should be very controlled when adjusting the pressure values. Because a small pressure change to balance blood oxygenation may result in PM, a complication with very high mortality. In our study, no significant difference was found between the two groups in terms of MV parameters such as $PEEP_{max}$ and PIP_{max}. In this case, the following questions comes to mind: Why PM developed in patients whose intraalveolar pressure was not higher than other patients? Are the other factors rather than barotrauma due to mechanical ventilation more important for the development of PM? Although the answer is yes according to the results of this study, further studies with larger series are needed.The fact that there was no statistically significant difference between groups in terms of the duration of ICU hospitalization and mechanical ventilation time between the groups supports this hypothesis.

Limitations

Our single-center retrospective study has some limitations. The most important limitation is the small number of patients for both groups. However, the number of PM cases for a single center is considerably higher than similar examples in the literature, although it is actually regrettable. Since the medical treatments used for the treatment of COVID-19 in our hospital are limited, favipiravir is primarily mentioned in the study. The relationship between other medical treatments and PM may also be a subject for other studies. Since the cases in our study

had only single CT images, radiological evaluations were made with the available images. This may be considered as another limitation of the study.On the other hand, we think that this study is important because it is the first study to systematically evaluate pneumomediastinum, which is considered the most mortal complication of COVID-19 pneumonia, in all aspects. Although this was not the case in our hospital, intensive care specialists in most hospitals could not keep up with the incredible need for intensive care during the pandemic. During this period, intensive care patients were often followed by physicians from other specialities. However, especially patients with respiratory distress or deterioration in general condition were admitted to intensive care. We think that we can ignore this situation since almost all patients with COVID-19-related or intubation-related pneumomediastinum need intensive care.

CONCLUSION

As the result; the probability of PM which is a very rare condition in the course of COVID-19 pneumonia, is high in patients who have diffusely organizing pneumonia pattern, and those affected more than 75% of the total lung volume. In these patients, immunomodulatory and antiviral therapy and prone position should be started early, and damage at the alveolar level should be minimized. Thus, it may be possible to prevent pneumomediastinum, the most mortal complication of COVID-19 pneumonia.

Conflict of interest: The authors declare that there is no conflict of interest

Informed Consent: Patients were not required to give their informed consent for inclusion in this retrospective study, because we used anonymous clinical data and individual cannot be identified according to the data present.

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Availability of Data and Materials: The materials described in the manuscript will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Ethics Approval: The study protocol was approved by Acibadem University Clinical Research Ethics Committee (Date: 2021-03-10, Approval number: 2021-05/03). The study complied with the Declaration of Helsinki.

Author Contributions: Concept – D.E.T.S., E.G., D.Y.; Design - D.E.T.S., E.G., D.Y., C.E.K., O.D., I.O.A.; Supervision – D.E.T.S., C.E.K., D.Y., O.D., I.O.A.; Resource - D.E.T.S., E.G., N.E., S.K., I.D., A.N.S.; Materials - D.E.T.S., E.G., N.E., S.K., I.D., A.N.S.; Data Collection and/or Processing - D.E.T.S., E.G., N.E., S.K., I.D., A.N.S.; Analysis and/or Interpretation - D.E.T.S., E.G., N.E., S.K., I.D., A.N.S.; Literature Search - D.E.T.S., A.N.S.; Writing - D.E.T.S.; Critical Reviews - D.E.T.S., D.Y., C.E.K., O.D., I.O.A.

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Original Research

Evaluation of in Vitro Cytotoxic and Apoptotic Effect of Tarantula Cubensis Alcoholic Extract on Human Prostate Cancer Cells

Deniz Gul[1], Haci Ibrahim Cimen[2], Asuman Deveci Ozkan[3], Gamze Guney Eskiler[3], Huseyin Cakıroğlu[4], Yavuz Tarik Atik[1], Anil Erdik[5], Osman Kose[2], Hasan Salih Saglam[2], Ahmet Gokce[2]

[1]Department of Urology, Sakarya Training and Research Hospital, Sakarya, Turkey
[2]Department of Urology, Faculty of Medicine, Sakarya University, Sakarya, Turkey
[3]Department of Medical Biology, Faculty of Medicine, Sakarya University, Sakarya, Turkey
[4]Experimental Medicine Research and Application Centre, Sakarya University, Sakarya, Turkey
[5]Department of Urology, Sakarya Toyotasa Emergency Hospital, Sakarya, Turkey

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Correspondence
Deniz Gul, MD
Sakarya Training and Research Hospital, Department of Urology,
Address: Adnan Menderes Cd. Saglik Sk. No:195 Adapazari, Sakarya, Turkey
E-mail: dr.guldeniz@gmail.com

ABSTRACT

Objective: Prostate cancer (PCa) is the second most common cancer in men worldwide and few studies have been reported investigating the effects of homeopathic therapy on PCa. Tarantula cubensis alcoholic extract (TCAE), is used in veterinary medicine as homeopathic medicine and there are various studies about the therapeutic efficacy of TCAE in treating different diseases. However, studies about the efficacy of TCAE in cancer treatment are limited.

It aimed to investigate the therapeutic efficacy of TCAE, which is used as homeopathic medicine in PCa.

Methods: DU-145 and LNCaP cells were used as PCa cell lines, and HUVEC cells were used as control cell lines. The effect of TCAE (25, 50, 100 and 250 µM) on cell viability was evaluated by Water Soluble Tetrazolium Salts-1 (WST-1) analysis, and its apoptotic effects were assessed by Annexin V analysis and acridine orange staining.

Results: TCAE decreased the viability rates in DU-145 and LNCaP cells in a time-dependent manner ($p<0.01$). The lowest viability rates for DU-145 and LNCaP cells were determined as 62.76±4.21% and 55.68±1.84% at 250 and 25 µM doses, respectively, for 48 h ($p<0.01$). Moreover, TCAE did not induce any cytotoxic effect on HUVEC cells ($p<0.01$). Apoptotic cell rates were found as 30.45±0.78% and 45.02±1.32% in DU-145 and LNCaP cells at 250 and 25 µM TCAE, respectively ($p<0.01$). Furthermore, impaired cell/cytoplasm ratio, chromatin condensation, membrane blebbing, and vacuolar damage were observed in DU-145 and LNCaP cells.

Conclusion: TCAE exerts cytotoxic and apoptotic effects on PCa cells. Additionally, due to androgen receptor status, LNCaP cells were more sensitive than DU-145 cells. However, further molecular studies are needed to determine the potential of TCAE as a new chemotherapeutic agent in PCa.

Keywords: Apoptosis; DU-145; LNCaP; Prostate cancer; Tarantula cubensis alcoholic extract

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men worldwide [1]. Age, genetic, metabolic, hormonal and infectious-related factors and diet are considered to be risk factors associated with PCa, but the underlying causes of its onset and progression have not been fully elucidated [2]. There are different treatment options with or without combinations for localized disease and metastatic disease. All these treatment options have significant and severe side effects, and consequently, to avoid these side effects, different treatment investigations have become the focus of attention of researchers.

Homeopathic treatment is included in complementary and

alternative medicine practices. In this treatment, the principle is that ‘’a substance that can cause symptoms in a healthy person may promote self-healing in a person with a disease with similar symptoms’’ [3]. Few studies have been reported investigating the effects of homeopathic therapy in PCa. The treatment response to the different homeopathic agents used in most of these studies is controversial [4-6]. However, it has been reported that the homeopathic medicine has positive effects on PCa cells due to reducing cell proliferation [7].

Tarantula cubensis alcoholic extract (TCAE), used in veterinary medicine as homeopathic medicine, is obtained by processing the entire ‘Tarantula cubensis’ spider in 60% alcohol [8]. Many therapeutic effects have been described for TCAE, such as; anti-inflammatory, demarcating, antiphlogistic, necrotizing, and resorptive influences, and it is effective in wound healing [9] respectively, and 29% of those cured by the tarantula poison (Theranekron. Despite the underlying mechanisms of the TCAE effect is not clear, it is thought to activate the defense mechanism against inflammation and proliferation [10]. The remedy can separate healthy tissues at the cellular level with its demarcating effect, and rapid healing and epithelialization are provided with its regenerative effect [11]. With this regard, there are various studies in the literature about the therapeutic efficacy of TCAE in treating different diseases. It is effective in peripheral nerve [12], tendon [13] and open wound [14] healing. Clinical benefits have been reported in oral, skin and teat papillomatosis in animals [15-17]. On the other hand, studies about the efficacy of TCAE in cancer treatment are limited. The positive results of some in vivo or in vitro studies on breast and colon cancer increase the importance of TCAE in cancer treatment [18-21]. However, there is no study in the literature about the effect of TCAE on PCa. In this present study, we aimed to investigate the therapeutic efficacy of TCAE, which is a homeopathic medicine, in PCa.

Main Points;

- Prostate cancer is one of the most common cancers in men, and alternative methods with fewer side effects are worth investigating in its treatment.
- Tarantula cubensis alcoholic extract (TCAE) is a homeopathic drug used in veterinary medicine, has anti-inflammatory and antioxidant effects, and has shown antitumoral effects on various cancers.
- This study has shown that TCAE has significant anti-tumoral effectiveness on prostate cancer cells.
- The anti-tumoral activity of TCAE in prostate cancer cells has been demonstrated as having both cytotoxic and apoptotic effects on two different types of prostate cancer cells, suggesting that TCAE may be beneficial as an alternative option in the treatment of prostate cancer.

MATERIALS AND METHODS

Cell culture

In this study, DU-145 and LNCaP cells were used as PCa cells in all analyses, and human umbilical vein endothelial cells (HUVEC) were used as a control cell only in the viability assay. All cells were purchased from the American Type Culture Collection (ATCC). TCAE (Theranekron®) was commercially purchased from Richter Pharma AG. The DU-145 and LNCaP cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640, Gibco) medium, and HUVEC cells were grown in Dulbecco’s modified eagle medium (DMEM, Gibco) supplemented with 10% fetal bovine serum (FBS Thermo Fisher Scientific) and 1% penicillin/streptomycin (Gibco). All cells were incubated in a humidified incubator with 5% CO_2 at 37 °C.

Cell Viability Assay

To determine the cytotoxic effects of TCAE, a WST-1 cell viability assay was performed. For this purpose, an equal number of DU-145, LNCaP and HUVEC cells ($2x10^4$ cells/well) were seeded on a 96-well plate. After 24 h, the cells were treated with different concentrations of TCAE (25, 50, 100 and 250 µM) for 24 and 48 h. Following administration of TCAE, 10 µl of WST-1 reagent (Biovision) was added to each well with 100 µl medium and incubated at 37 °C for 30 min. After incubation time the absorbance values from the wells were obtained from the microplate reader (Allsheng) at 450nm. We selected the most effective exposure time and concentration of TCAE for further analysis. Each experiment was performed in triplicate.

Annexin V Assay

The apoptotic effects of TCAE on PCa cells were determined with Muse Annexin V & Dead Cell Assay. For this purpose, an equal number of DU-145 and LNCaP cells ($1x10^5$ cells/well) were seeded on a 6-well plate. After 24 h, the cells were treated with different concentrations of TCAE (25, 50, 100 and 250 µM) for 48 h. Following administration of TCAE, the cells were centrifuged at 1200 rpm and the cell pellet was washed with 1 ml of PBS twice and stained with MuseTM Annexin V & Dead Cell Assay Kit (Millipore) at room temperature for 30 min. After 30

min incubation, the stained cells were analyzed with the Muse Cell Analyzer (Millipore) according to the instructions. Each experiment was performed in triplicate.

Acridine Orange (AO) Staining

To further analyze the apoptotic effects of TCAE on PCa cells, the cell morphology was observed with AO staining. For this purpose, an equal number of DU-145 and LNCaP cells ($1x10^5$ cells/well) were seeded on a 6-well plate. After 24 h, the cells were treated with different concentrations of TCAE (25, 50, 100 and 250 µM) for 48 h. Following administration of TCAE, the cells were fixed with 1 ml of 4% paraformaldehyde (PFA) and stained with 1 ml of AO (100 mg/ml) dye at room temperature and dark for 30 minutes. Stained cells were visualized with EVOS FL Cell Imaging System (Thermo Fisher Scientific) according to the instructions.

Statistical Analysis

SPSS 22.0 (IBM, USA) was used for statistical analysis, and the results were expressed as the mean ± standard deviation of three independent experiments. One-way analysis of variance (ANOVA) followed by Tukey's test was used for multiple comparisons. The relationship between drug dose and viability rates was evaluated with the Pearson correlation test, and p-values less than 0.05 were considered statistically significant.

RESULTS

Evaluation of the Cytotoxic Effects of TCAE on PCa Cells

WST-1 was performed in DU-145 and LNCaP also HUVEC cells to determine the cytotoxic effect of TCAE on PCa cells. Our results showed that TCAE had a cytotoxic effect on two different types of PCa cells. According to our results, TCAE decreases the viability of cells time-dependently ($p<0.01$, Figure 1). After 48 h incubation with 25, 50, 100, and 250 µM TCAE, the viability of DU-145 cells significantly reduced to 68.13±1.93%, 68.15±1.72%, 66.14±4.76% and 62.76±4.21%, respectively ($p<0.01$, Figure 1A). Additionally, the viability of LNCaP cells reduced to 55.68±1,84%, 57.11±2.06%, 59.44±0.66%, and 62.54±0.78%, respectively for 48 h ($p<0.01$, Figure 1B). Furthermore, after incubation with TCAE (25, 50, 100, 250 µM) for 48 h, the proliferation of HUVEC cells was detected as 88.63±0.09%, 113.94±0.41%, 111.74±1,30% and 99.04±1.02%, respectively ($p<0.01$, Figure 1C). Therefore, TCAE treatment for 48 hours was more effective than 24-hour treatment in both DU-145 and LNCaP cells and did not cytotoxicity in HUVEC cells ($p<0.01$). In addition, the most effective dose of TCAE was 250 and 25 µM in DU-145 cells and hormone-sensitive LNCaP cells, respectively. These findings showed that LNCaP cells were more sensitive to TCAE than DU-145 cells.

Evaluation of the Apoptotic Effects of TCAE on PCa Cells

Annexin V analysis was performed in DU-145 and LNCaP cell lines to determine the effect of TCAE on apoptotic cell death. The obtained results demonstrated that TCAE increased the percentage of apoptotic cells in different types of PCa cells and showed a significant increase, especially in the percentage of early apoptotic cells ($p<0.01$, Figure 2). After 48 h of incubation with 25, 50, 100, and 250 µM TCAE, and the percentage of total apoptotic cells amounted to 22.54±1.00%, 23.53±1.12%, 25.86±0.44%, and 29.80±0.39% in DU-145 cells, respectively ($p<0.01$, Figure 2A, 2C). Additionally; 25, 50, 100, 250 µM TCAE concentrations increased the percentage of total apoptotic cells (44.06±1.58%, 36.65±0.84%, 36.99±0.73%, and 28.43±2.37% respectively) in LNcaP cells for 48 h ($p<0.01$, Figure 2B, 2C).

Evaluation of the Morphological Effects of TCAE on PCa Cells

AO staining was performed to demonstrate the morphological changes caused by TCAE in PCa cells associated with apoptotic cell death. Our results revealed that TCAE caused morphological changes associated with apoptotic cell death in two different types of PCa cells (Figure 3). At the end of 48 hours, impaired cell/cytoplasm ratio, chromatin condensation, membrane blebbing and vacuolar damage were observed in PCa cells due to the increasing concentration of TCAE compared to the control group (Figure 3). However, TCAE caused more apoptotic changes in the cell morphology of LNCaP cells than DU-145 cells.

DISCUSSION

The anti-cancer effects of TCAE have been shown in clinical veterinary medicine. However, it has not yet been fully elucidated the underlying molecular mechanisms of TCAE in human cancers. Although there are various investigations on its effects on breast and colon cancer, there has been no study on its impact on PCa. In this study, for the first time, the cytotoxic and apoptotic effects of TCAE on two different types of PCa cells were determined in vitro. The findings showed that TCAE decreased viability rates and increased apoptotic cell rates in PCa cells. Thus, with the present study, data supporting that TCAE may be a potential anti-cancer therapeutic agent in the treatment of PCa were obtained.

Clinical observations and research on the homeopathic effects of TCAE have primarily been on wound healing. It has been shown that TCAE stimulates and accelerates epithelization [11,14] and has anti-inflammatory effects on animals [22]. Makav et al. [23] reported that TCAE has therapeutic efficacy in an experimentally generated gastric ulcer model in rats, exhibits lower gastric erosion and better efficacy than ranitidine, and causes a decrease in the levels of pro-inflammatory cytokines IL-1β and IL-6.

Few studies are evaluating the effects of TCAE on the genitals. It has been shown that TCAE accelerates postpartum uterine regeneration in cows [24]. Kozlu et al. [25] suggest that TCAE may have remedial effects in an experimentally generated ischemia-reperfusion injury model in the rat ovary. It has also been reported that TCAE causes atrophy in endometriosis foci in an experimentally established endometriosis model in rats [26] and the results of this study may suggest that TCAE may also have hormonal effects. However, its mechanism of action is unclear.

Studies about cancer treatment have shown that TCAE is effective in treating some types of cancer (breast and colon) [19,20,27]. However, the first study that pioneered and guided these studies was reported by Koch and Stein in 1980. In this study, TCAE inhibits tumor growth by forming a demarcation line in canine mammary tumors [28]. More recently, Gultiken and Vural [18] investigated the efficacy of TCAE in canine mammary tumors and stated that TCAE administration is beneficial in terms of tumor regression, recurrence and metastasis. In addition, Er et al. [21], in their study investigating the effects of TCAE in an experimentally generated colon cancer model in rats, is reported that TCAE may have an anti-cancer effect and increased TNF-α level.

In the literature, studies evaluating the effects of homeopathic medicines on PCa are limited, and the first study was reported by Jonas et al. in 2006. In this study, five different homeopathic drugs widely used have no effect on cell viability, gene expression, and apoptosis in DU-145, LNCaP and MAT-LyLu PCa cells. However, in the same study, in rats injected with MAT-LyLu PCa cells, a reduction in tumor incidence and volume and an increase in apoptotic cell death are reported after treatment with homeopathic drugs [4]clinical and laboratory research has been equivocal, and no rigorous research has been done on cancer. In 1999, the US National Cancer Institute

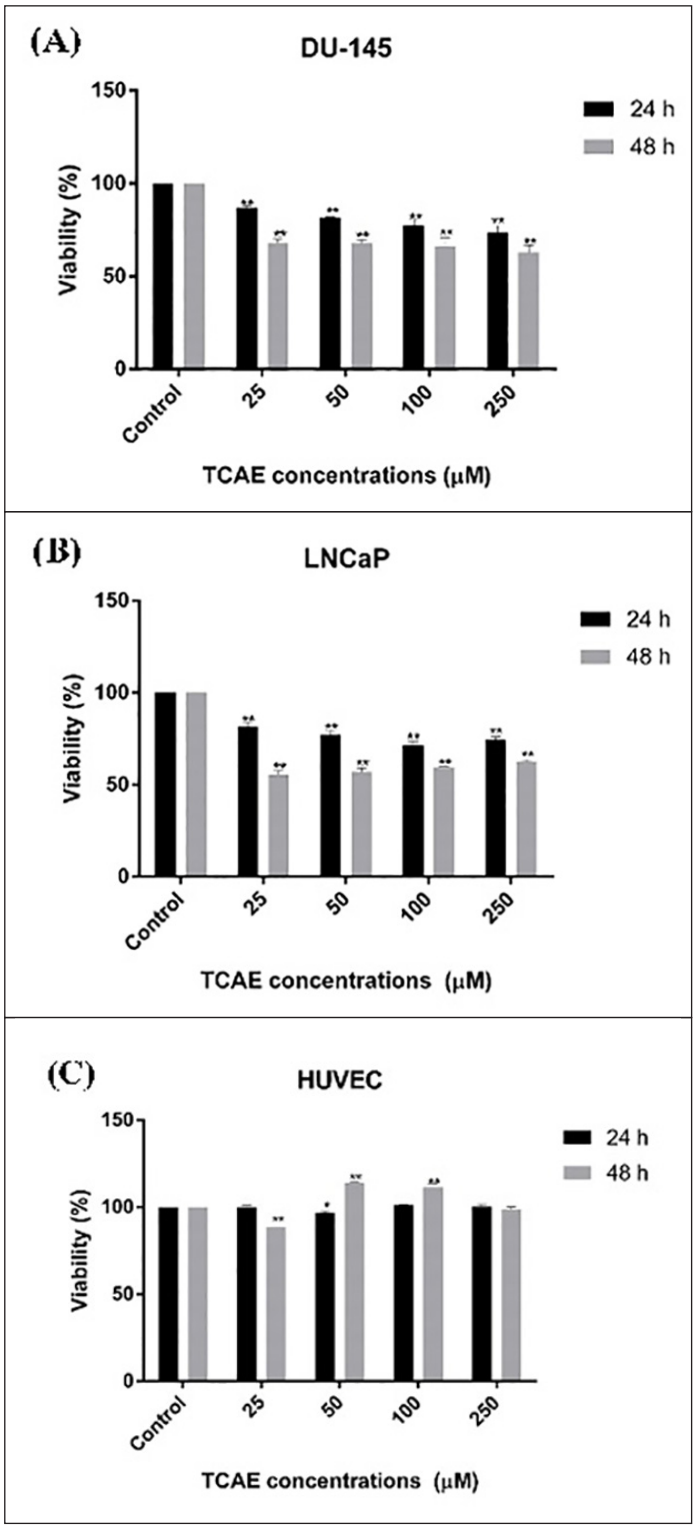

Figure 1. The cytotoxic effect of TCAE on DU-145, LNCaP and HUVEC cells. Following administration of TCAE (25, 50, 100 and 250 μM) for 24 and 48 hours, the viability rates of (A) DU-145, (B) LNCaP and (C) HUVEC cells were determined with WST-1 viability assay. (TCAE: Tarantula cubensis alcoholic extract, WST-1: Water Soluble Tetrazolium Salts-1, μM: micromolar *:$p<0.05$; **:$p<0.01$).

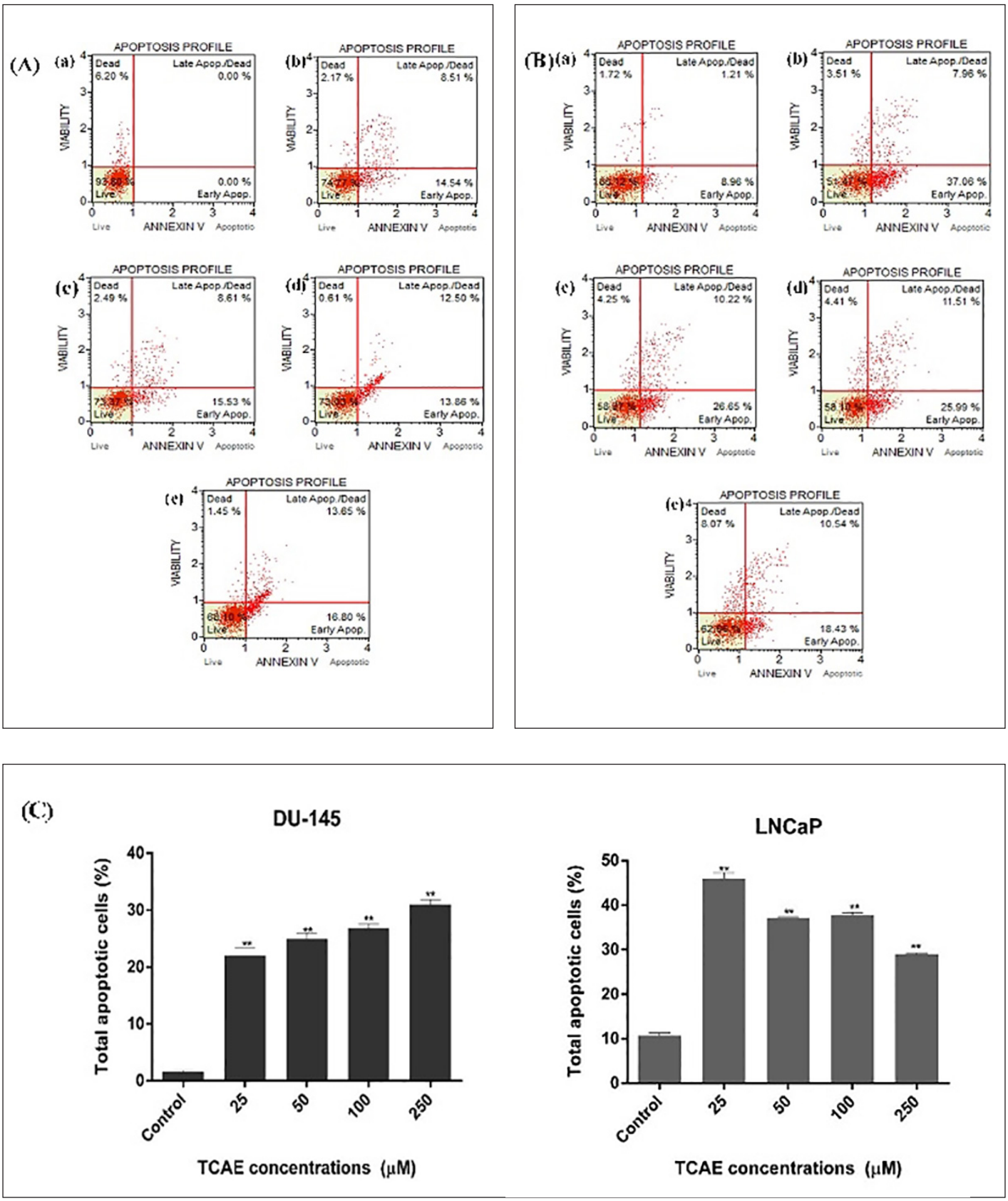

Figure 2. The results of Annexin V analysis. (A) DU-145 and (B) cells treated with (a) control, (b) 25 μM, (c) 50 μM, (d) 100 μM ve (e) 250 μM TCAE for 48h. (C) Statistical comparisons of the percentage of TCAE induced total apoptotic cell death in DU-145 and LNCaP cells. (TCAE: Tarantula cubensis alcoholic extract, μM: micromolar, *:p<0.05; **:p<0.01).

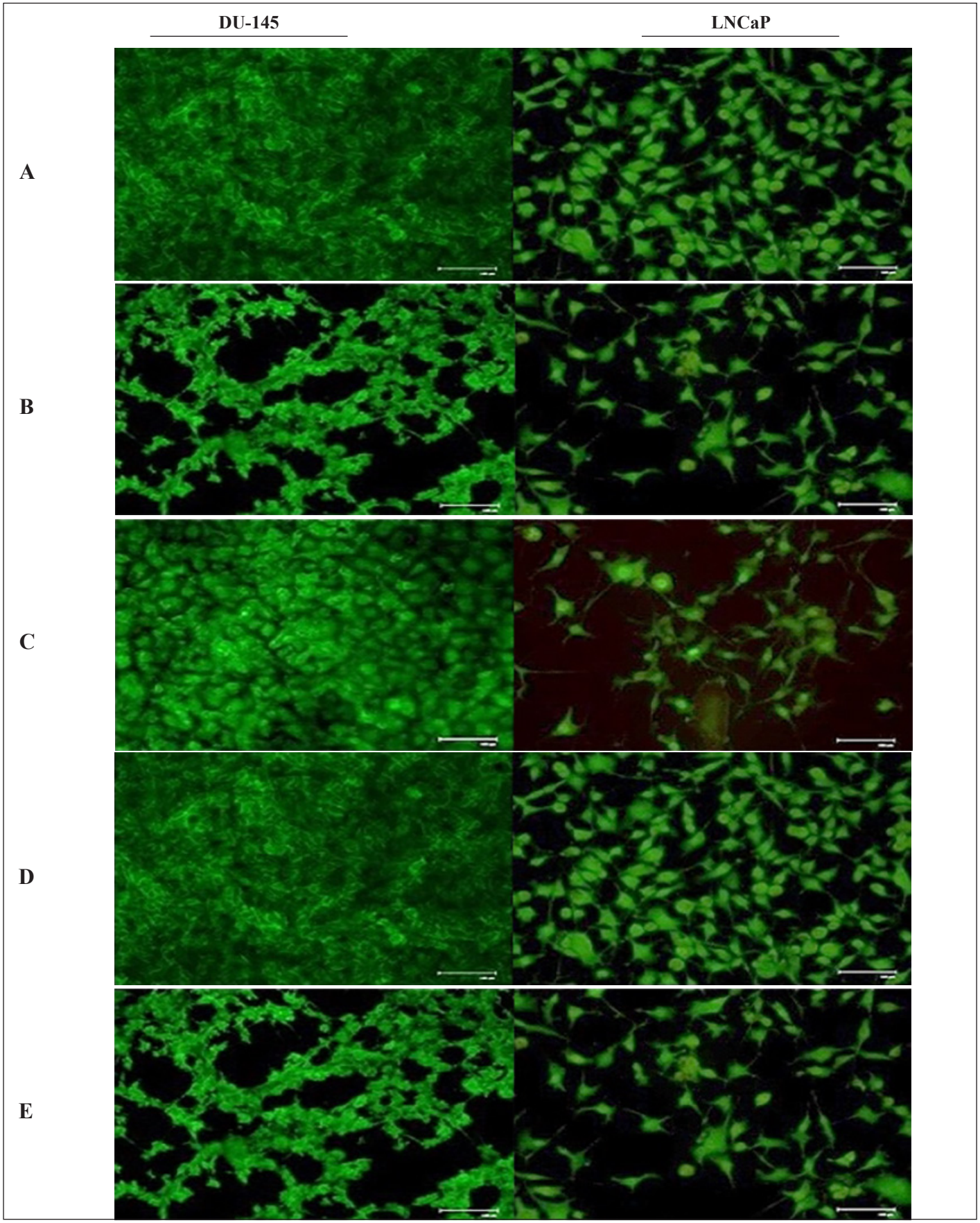

Figure 3. The effects of TCAE on cell morphology of DU-145 and LNCaP cells. The cells were treated with (A) control, (B) 25 μM, (C) 50 μM, (D) 100 μM ve (E) 250 μM TCAE for 48h. (TCAE: Tarantula cubensis alcoholic extract, μM: micromolar)

evaluated the effects of homeopathic treatment of cancer from a clinic in India and has released a request for protocols to conduct further research into this treatment. Therefore, the authors conducted a series of carefully controlled laboratory studies evaluating the effects of commonly used homeopathic remedies in cell and animal models of prostate cancer. STUDY DESIGN: One hundred male Copenhagen rats were randomly assigned to either treatment or control groups after inoculation with prostate tumor cells. METHODS: Prostate tumor cells DU-145, LNCaP, and MAT-LyLu were exposed to 5 homeopathic remedies. Male Copenhagen rats were injected with MAT-LyLu cells and exposed to the same homeopathic remedies for 5 weeks. In vitro outcomes included tumor cell viability and apoptosis gene expression. In vivo outcomes included tumor incidence, volume, weight, total mortality, proliferating cell nuclear antigen (PCNA. In subsequent studies, Thangapazham et al. [5] do not detect significant changes in apoptotic genes and cytokine levels after homeopathic treatment in an animal model of PCa. Also, homeopathic drug administration to PCa cells (DU-145, LNCaP, MAT-LyLu) does not affect cell growth and viability and does not cause changes in apoptotic gene expression [6]. On the other hand, MacLaughlin et al. [7] stated that 'sabal serrulata' used in homeopathic treatment causes a reduction in PC-3 and DU-145 PCa cells with the rate of 33% and 23%, respectively.

In our study, TCAE reduced the viability of both PCa cell lines in a time-dependent manner, and the viability rates of LNCaP cells were lower than DU-145 cells for 48 hours. The most effective dose was found to be 25 μM in LNCaP cells and 250 μM in DU-145 cells. Furthermore, TCAE did not have any cytotoxic effects on HUVEC cells. The increase in the viability of HUVEC cells at increasing doses of TCAE suggests that it may cause a proliferative effect on non-carcinogenic cells. Er et al. [19] reported that TCAE has an inhibitory effect on the proliferation of the MCF-7 breast cancer cell line, and this effect increases in a concentration and time-dependent manner. In another in vitro study, Ghasemi-Dizgah et al. [20] investigated the impact of TCAE on different cell types (MCF-7 and HN-5 cancer cell lines and HEK293 control cells). TCAE decreases cell proliferation in a dose-dependent manner. In addition, its cytotoxic effect on MCF-7 and HN-5 is higher than HEK293. These studies support our findings, and TCAE did not show any cytotoxic effect on healthy cells.

Furthermore, the highest apoptotic cell rates were obtained in DU-145 and LNCaP cells, at 250 and 25 μM TCAE concentrations, respectively. These findings were consistent with the results of the viability assay. In addition, the total apoptotic cell rates were higher in LNCaP cells than in DU-145 cells. Therefore, hormone-sensitive PCa may be more sensitive to apoptosis-targeted therapies. Several studies have shown the apoptotic effect of TCAE on cancer cells. Er et al. [19] reported that TCAE administration for 6 hours increases apoptosis in MCF-7 cells. In canine mammary tumors, the rate of apoptotic cells has increased following TCAE administration [27]. Ghasemi-Dizgah et al. [20] stated that TCA treatment induces DNA fragmentation and caspase-3 activity in the cells.

Limitations

This study has a few limitations. Protein and gene expression analyses were not performed and therefore it could not be determined which apoptotic pathways play a role. In addition, the lack of testing on animal models is another limitation.

CONCLUSION

In conclusion, TCAE showed an anti-cancer effect on PCa cells by inducing apoptosis in our study. However, further investigations of the underlying molecular mechanisms of TCAE-mediated apoptosis in PCa cells are required. Furthermore, TCAE alone cannot achieve sufficient efficacy in the treatment of PCa. Therefore, combination treatment studies are needed to evaluate the possible synergistic effects of TCAE with chemotherapy drugs. Thus, TCAE treatment may reduce the side effects of chemotherapy drugs in PCa treatment.

Conflict of Interest: The authors declare that they have no conflict of interest in the publication.

Informed Consent: Informed consent was not obtained.

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Ethical Approval: Informed consent was not obtained.

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Original Research

Comparative Study, Walant vs Axillary Block in Carpal Tunnel Surgery

Zafer Soydan [1], İsmail Bülent Özçelik [2]

[1] Department of Orthopedics and Traumatology, Nisantası University, Bht Clinic İstanbul Tema Hastanesi, Turkey
[2] Department of Hand Surgery, İstanbul Yeni Yuzyil University Gaziosmanpaşa Hospital, Turkey

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Correspondence
Zafer Soydan, MD
Address: Nisantası University, Bhtclinic İstanbul Tema Hastanesi, Orthopedics and Traumatology Atakent Mh 4.Cadde No 36, PC 34307 Kucukcekmece/İstanbul/ Turkey
E-mail: zsoydan@gmail.com

ABSTRACT

Objective: Wide awake local anesthesia no tourniquet (WALANT) is a local anesthetic technique that, in theory, reduces costs and surgical waiting periods. The purpose of this study was to compare axillary block (AXB) with WALANT in terms of pain scores, duration of hospital stay, and hand function in patients who underwent CTR surgery.

Methods: Between January 2015 and February 2020, a retrospective analysis was conducted on the outcomes of 410 patients who underwent CTS surgery. The Walant technique was utilized on 210 patients, while the AXB technique was utilized on 200 patients. These two groups were compared regarding operative time, hospital stay, VAS score at specific intervals before and after surgery, and hand function recovery.

Results: The mean operation time is 11 min (8-18) for the WALANT group and 12 min (5-34) for the AXB group. The average time of the length of hospitalization is 4.2 hours (2-6) for the WALANT and 14.2 hours (9-26) for the AXB groups. The mean hospitalization time and the VAS scores of the WALANT group are significantly less than the AXB group (p=0.02 and p=0.03 respectively). The percentages of being able to use their hands compared to their nonoperative hands were evaluated. These rates were higher in the WALANT group than in the AXB group (65-75% vs. 45-60%).

Conclusion: Increased patient comfort was associated with the WALANT technique. It is superior to AXB in terms of patient satisfaction, postoperative long-term pain management, and hand function recovery. Assuming all safety recommendations are adhered to, the WALANT is an alternative to tourniquets in CTS surgeries for obtaining a bloodless surgical field without the discomfort of tourniquet application.

Keywords: Carpal Tunnel Surgery, WALANT, Axillary Block, VAS, patient satisfaction.

INTRODUCTION

Carpal Tunnel Syndrome (CTS) is the most frequent form of upper-limb compression neuropathy [1]. It is typically more prevalent in individuals over the age of 40. There are numerous techniques for carpal tunnel release (CTR), including open, endoscopic, and ultrasound-guided procedures [2,3].

The Wide Awake Local Anesthesia with No Tourniquet (WALANT) technique has emerged as a popular and effective alternative to sedating anesthetic techniques or axillary blocks that requires monitoring for carpal tunnel surgery [4]. However, the literature lacks data regarding patient satisfaction with regard to anesthesia type and surgery location [5].

In carpal tunnel release surgery, a bleeding-free environment is especially needed for clear visualization of the motor branch

and adequate nerve release. Until 2015, all carpal tunnel release surgeries performed in our clinic were performed under axillary anesthesia with a tourniquet. Generally, in dialysis patients, if there was a fistula in the same arm, local anesthesia was applied. After 2016, operations were performed with WALANT in CTS operations. Clinical diagnosis was based on the presence of symptoms including paresthesia or numbness (or both) in the median nerve distribution, nocturnal paresthesias, aching, weakness, and atrophy of the thenar eminence [6]. This study's objective was to compare axillary block (AXB) with WALANT in patients who underwent CTR surgery in terms of pain scores, length of hospital stay, and hand function.

MATERIALS AND METHODS

This was a retrospective, single-center, single-surgeon observational study conducted at the university hospital. This investigation was approved by the Institutional Review Board (Protocol No. 2023/23/21). Informed consent was obtained from all participants. We included a total of 410 patients who underwent CTR between January 1, 2015 and February 28, 2020. This study excluded pregnant and postpartum women, patients who refused the terms of the consent statement, and patients who stated they had previously undergone hand or wrist surgery. The standard mini-open incision for carpal tunnel release was performed. According to the anesthetic technique used to treat these 410 patients, they were divided into two groups of 210 and 200 patients each. WALANT contained 100 ml of 1% lignocaine, 1 ml of epinephrine (1:1000), and 10 ml of 8.4% sodium bicarbonate for a total of 111 ml. 10 ml of WALANT is used for each patient. The AXB group consisted of 200 patients (140 females and 60 males) with a mean age of 52.7 years (40–70). In the Walant group, there were 210 patients (144 females and 66 males) with a mean age range of 54.6 (42–75) years. The duration of hospitalization was determined, and VAS assessment of postoperative pain was performed. VAS was performed four times on each patient: per-operatively, two hours after surgery, twenty-four hours after surgery, and forty-eight hours after surgery. In the 24-48 hour patient reported outcomes, the percentage of using the hand on the operated side compared to the other hand was questioned. Out-of-hospital pain questioning of the patients was performed by telephone contact. The results between AXB group and WALANT group were compared. The chi-square test was used to analyze the relationship between the categorical variables and the results from both groups. To compare the groups in relation to continuous variables, the Student's t test (parametric) or the Mann-Whitney U test was utilized. The significance level was set at 5%.

Main Points;

- The WALANT technique is superior to AXB in carpal tunnel surgery for both the patient and the surgeon.
- In the postoperative period, WALANT is associated with less pain and greater motion gain.
- WALANT is more advantageous than AXB in terms of length of hospital stay and hospital costs.

RESULTS

Demographics is given in Table 1. The mean operative time was 12 minutes (min: 5, max: 34) for the entire cohort: 11 minutes (min: 8, max: 18) for the WALANT group, and 13 minutes (min: 7, max: 34) for the AXB group. With AXB, the average length of hospitalization was 14.2 hours (9–26 hours), while with WALANT, it was 4.2 hours (2–6 hours). By employing a VAS, postoperative pain was evaluated. With AXB, the per-operative VAS score was 0.2 (0–0.5), whereas with WALANT, it was 0.3 (0–0.6). At two hours postoperatively, the VAS score was 0 for AXB and 0 for WALANT. At 24 hours, the VAS score with AXB was 1.2 (0.5–4) and with WALANT it was 0.5 (0–2). At 48 hours, the VAS score with AXB was 0.8 (0–2) and with WALANT it was 0.4 (0–1). With WALANT, the patients were able to use the operated hand. 65% at 24 hours and 75% at 48 hours, compared to the other hand. The mean hospitalization time and the VAS scores of the WALANT group were significantly lower than those of the AXB group ($p = 0.02$ and $p = 0.03$ respectively). With AXB, the patients were able to use their operated hand at 24 hours and 60% at 48 hours compared to the other hand (See Table 2).

DISCUSSION

It has been reported that Walant is a potent and comfortable analgesic for patients [7,8] as well as handy for surgeons and healthcare systems [9,10]. It has even enabled the relocation of such surgeries outside the main surgery center with no rise in surgical risk, no change in clinical results, and a reduction in cost [11-13]. In our study, WALANT produced more favorable results compared to AXB in terms of pain scores, hand function, and hospitalization length of time. Upon comparing the results, we found that the per-operative pain VAS evaluation with WALANT was slightly higher than with axillary anesthesia. We

Table 1. Demographics of Cohort.

	WALANT	AXB	Total	p-value
Patient number	210	200	410	
Age (years)	54.6 (42-75)	52.7 (40-70)	53.1 (40-75)	0.87
Sex (Female/Male)	144/66	140/60	284/126	0.64
Mean duration of procedure (min)	11 (8-18)	13 (7-34)	12 (7-34)	0.02

Table 2. Comparison of the results of two groups according to VAS score and hand functions.

	WALANT	Axiller
Number of Patients	210	200
Time of Hospitalization (hours)	4.2(2-6)	14.2 (9-26)
VAS Pre-op	0.3(0-0.6)	0.2(0-0.5)
VAS Post op 2h	0	0
VAS Post op 24h	0.5(0-2)	1.2(0.5-4)
VAS Post op 48h	0.4(0-1)	0.8(0-2)
Rate of hand functions (post op 24h)	65%	45%
Rate of hand functions (post op 48h)	75%	60%

believe this is the result of the local injection. At 2-hour controls, axillary anesthesia and WALANT did not differ significantly from one another. At 24 and 48 hours, the VAS evaluation of the WALANT group was superior to axillary anesthesia. These results are also consistent with the literature. Boukebous et al reported patient satisfaction appeared to be same between WALANT and AXB. WALANT found as effective and safe as AXB [5]. Although epinephrine-induced digital ischemias and tissue necrosis have been reported in the medical literature and are typically attributable to dosing errors [14], we did not observe any complications in our patients. No peripheral venous access or monitoring is required when administering safe doses of local anesthetic [15]. Reportedly, advantages such as not requiring anesthesia consultation, less hospital time, not requiring fasting prior to the procedure, and establishing a more compliant relationship with the physician enhance patient satisfaction [16]. We believe that these previously reported factors may be associated with patient satisfaction in our study.

In the medical literature, tourniquet use has been linked to instances of transient pain, paresthesia, transient nerve damage, and even complete nerve paralysis [17,18]. It was the primary cause of discomfort. It is therefore advised to avoid tourniquet use if hemostasis can be achieved. Walant's epinephrine is vasoconstrictive and has a hemostatic effect [19]. In their study, Gunasagaran et al. demonstrated that the local anesthetic plus tourniquet group was not superior to the WALANT group in terms of less bleeding [20]. In our study, a tourniquet was applied to all patients who underwent AXB, and postoperative bleeding was controlled. All patients were given a drain, which was removed 24 hours following surgery. Patients who underwent WALANT were not administered drain and we did not encounter any bleeding problems in in WALANT group of our study. Ecchymosis extending from the arm to the elbow region after axillary anesthesia was seen in 4 patients. Skin problems around the tourniquet due to tourniquet compression were observed in 2 patients. Patients reported that these problems had a negative effect on patient satisfaction. Our outcomes are consistent with recent research.

Limitations

The limitations of the study were the short follow up time and retrospective in which satisfaction and pain perception may change over time. Prospective long term follow up study needed.

CONCLUSION

The WALANT technique was associated with increased patient comfort. It is more effective than AXB in patient satisfaction,

postoperative long-term pain management, and recovery of hand functions. Tourniquets were the most significant cause of discomfort during surgical procedures. Therefore, WALANT is a choice to tourniquets for achieving a bloodless surgical area during CTS procedures without experiencing the discomfort of tourniquet deployment, assuming all safety suggestions were adhered to.

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All authors have made substantial contributions in the interpretation of data, revising the article critically and all approved of the final version for submission.

All authors disclosed no relevant relationships.

Ethical Approval: The study was initiated following approval from the Ethics Committee of Nişantaşı University (approval number 2023/23/21, Date: 2023-06-12), and all procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki.

Authors' Contribution

Concept – Z.S., I.B.Ö; Design– Z.S Supervision – Z Z.S., I.B.Ö; Materials – Z.S., I.B.Ö; Data Collection and/or Processing – Z.S., I.B.Ö.; Analysis and/or Interpretation - Z.S., I.B.Ö.; Literature Review – Z.S., I.B.Ö.; Writing – Z.S., I.B.Ö; Critical Review - Z.S., I.B.Ö.

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Original Research

The Effect of the Age at Seizure Onset on Seizure Resistance in Tuberosclerosis Patients

Saliha Yavuz Eravci[1], Sevinç Çelik[2], Burcu Çalişkan[1], Fayize Maden Bedel[2], Abdullah Canbal[1], Nagehan Bilgeç[2], Hayriye Nermin Keçeci[2], Ahmet Sami Güven[1], Hüseyin Çaksen[1]

[1] Department of Child Neuorology, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey
[2] Department of Child Genetics, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey

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Correspondence
Saliha Yavuz Eravcı, MD
Address: Yunus Emre, Akyokuş Sk., Meram Konya / Turkey
E-mail: salihayavuz88@gmail.com

ABSTRACT

Objective: To evaluate the clinical status of epilepsy, which is extremely widespread in tuberosclerosis patients and the findings and characteristics of a pediatric case series.

Methods: The study included pediatric patients diagnosed with tuberosclerosis from clinical or genetic examination who were followed up between 2015 and 2022 in the Pediatric Neurology and Pediatric Genetics Clinics of Necmettin Erbakan University Meram Medical Faculty Hospital. A retrospective examination was made of the clinical characteristics of the patients, the electroencepahalography (EEG) reports, and radiological findings (magnetic resonance imaging [MRI], ultrasonography, echocardiography). The patients were separated into two groups of monotherapy and polytherapy according to the number of drugs used, and the groups were compared in respect of the time of onset of epilepsy. The patients were also categorised according to the presence of cortical tuber and subependymal nodule and these groups were compared in respect of the presence of epilepsy.

Results: The 27 patients comprised 18 (66.6%) males and 9 (33.4%) females. Complaints on presentation were seizure and skin patches in 25 (92.5%) cases and only skin patches in 2 (7.5%). The most common finding determined on MRI was the combination of subependymal nodule and cortical tuber (51.8%). Autism spectrum disorder was present in 5 (18.5%) patients and mental retardation in 16 (59%). The age at onset of epilepsy was earlier in the polytherapy group [5±4.75 (1-18) months] than in the monotherapy group [8.0±16 (4-36) months] ($p=0.032$). The rates of presence of cortical tuber and subependymal nodule were similar in respect of the time of onset of epilepsy ($p>0.05$).

Conclusion: The early onset of epilepsy in tubersclerosis patients indicates that it may have a resistant course and there may be a need for polytherapy. There may also be accompanying neuropsychiatric retardation in these patients. The clinical status of epilepsy in tuberosclerosis was found to be similar in the cortical tuber and subependymal nodule groups.

Keywords: Tuberosclerosis, epilepsy, polytherapy, cortical tuber

INTRODUCTION

Tuberosclerosis complex (TSC), which was first described by Bourneville in 1880, is a multi-systemic disease that is seen in 1 in 6000 live births [1]. The organs most affected are the skin, brain, kidneys, heart, eyes, and lungs. A broad spectrum of manifestations of the disease can be seen such as skin, heart,

brain and kidney-origin tumours, seizures and autism spectrum disorder. There are two genetic mechanisms for tuberosclerosis; TSC1 gene on chromosome 9q34 and TSC2 gene on chromosome 16p33. The protein named hamartin encodes TSC1 gene, and tuberin encodes TSC2 gene. In the physiology of a normal healthy individual, hamartin and tuberin function together, and any dysfunction in either of these causes the formation of hamartoma in tuberosclerosis [2]. Findings of the disease can show variability even within the same family. Familial cases are inherited as autosomal dominant, but the vast majority of cases occur as a result of de novo mutation [3].

Epilepsy is the most frequently seen neurological disorder in tubersclerosis patients. All seizure types may be seen in patients with epilepsy and the majority of seizures are resistant to anti-epileptic treatment [4]. The glial neurons in the cortical tubers are thought to play a role in the epileptogenesis of tuberosclerosis [5]. That regions corresponding to cortical tubers are encountered as epileptic focus on electroencephalography (EEG) supports this view. In a previous study that examined the EEGs of tuberosclerosis patients, the EEG was disrupted in approximately three-quarters of the case series, a smaller proportion was normal, and there was seen to be slowing down on the EEG of a few [6]. In the treatment of epilepsy in tuberosclerosis, many anti-epileptic treatments and non-pharmacological treatments such as ketogenic diet can be used. The International Tubersclerosis Consensus decision made in 2012 recommended vigabatrin as the first option for infants, and anti-epileptic drugs that are effective on gamma aminobutyric acid (GABA) for older patients [7]. The aim of this study was to evaluate the clinical characteristics of epilepsy, in tuberosclerosis patients followed up in our clinic and to examine the relationship between these characteristics and other clinical findings.

Main Points;

- Epilepsy clinic is frequent in tuberosclerosis patients and the present study is focusing on this clinic in our paediatric case series.
- This study reveales that early onset of epilepsy in tubersclerosis patients may have a more resistant course and there may be a need for polytherapy
- The clinical status of epilepsy in tuberosclerosis is similar in patients with cortical tuber and subependymal nodüle.

MATERIALS AND METHODS

Approval for the study was granted by the Local Ethics Committee (Aprovval no:2022/490) and all procedures were performed in compliance with the Helsinki Declaration.

A total of 45 patients were identified who were diagnosed with tuberosclerosis between 2015 and 2022 in the Pediatric Neurology and Pediatric Genetics Clinics of Necmettin Erbakan University Meram Medical Faculty Hospital. All the patients included were aged 2-18 years with at least 2 years of follow-up. Patients were excluded from the study if they were diagnosed and followed up at another centre. The study included 27 patients who met the study criteria.

The e-medical records system of the hospital were scanned retrospectively for the demographic data of the patients (age, gender, family history, etc.) clinical data (the presence of seizures, anti-epileptic drugs used, age at onset of seizures, physical examination findings, etc.), and the findings of electroencepahalography (EEG), abdominal ultrasonography (USG), echocardiography (ECHO) and brain magnetic resonance imaging (MRI).

The diagnosis of tuberosclerosis in all the patients was made based on the International Tuberosclerosis Consensus criteria published in 2012 [8]. In 17 patients, there was also a genetic confirmation test. Seizures which could not be controlled with two well tolerated and appropriately selected drugs (monotherapy or combination) for an appropriate treatment were evaluated as resistant epilepsy [9]. The patients in this study receiving anti-epileptic treatment were separated into two groups as those receiving polytherapy (2 or more drugs) or monotherapy (a single drug). The seizure types were classified as focal, generalised [10].

Pathologies such as the presence of renal cortical cyst and the presence of renal angiomyolipoma in the abdomen were evaluated radiologically with USG. On brain MRI, the presence of conditions such as cortical tuber (hamartoma) and/or subependymal nodule, and hydrocephaly in the brain were evaluated.

The data of the present study were analyzed statistically using SPSS version 22 software (SPSS, Chicago, IL, USA). In the descriptive analysis of the data, continuous variables were presented as median and interquartile range (IQR), minimum

and maximum values, and categorical variables as frequency (n) and percentage (%). The tuberosclerosis patients were classified according to seizure treatment with monotherapy (Group 1) or polytherapy (Group 2) and the groups were compared in respect of age at onset of seizures.The study population was also divided according to the presence of cortical tuber and subependymal nodule, and these two groups were compared in respect of the clinical status of seizures. Conformity of the data to normal distribution was evaluated using the Kolmogorov–Smirnov test and according to the results, non-parametric tests were used. The Mann Whitney U-test was used for the comparisons of the numerical data of the age of onset of seizures and the Pearson Chi square test was used for the comparison of the categorical data of the clinical presence of epilepsy. A value of $p<0.05$ was considered statistically significant throughout the study.

RESULTS

The 27 patients comprised 18 (66.6%) males and 9 (33.4%) females, with a mean age of 10.0±8.5 years (range, 3-17 years). The mean age at presentation was 6.0±7.0 months and the mean age at onset of seizures was 5.0±6.0 months (1-36 months). The most common complaint on presentation was seizure (n: 25, 92.5%). Epilepsy started within the first 6 months of life in 15 (55.5%) patients (Figure 1). The seizures were in the form of focal seizure in 17 (68%) patients, and generalised seizures in 8 (32%). Of the patients receiving anti-epileptic treatment, resistant seizures were present in 11 (44%) patients, and the seizures were kept under control with a single drug in 14 (56%) patients.

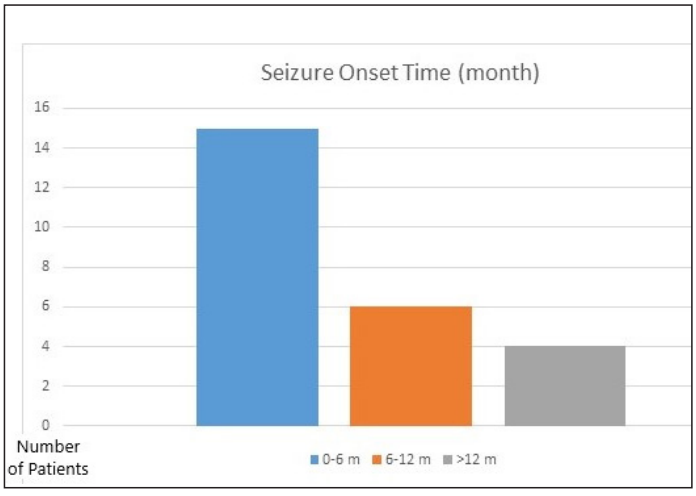

Figure 1. The number of patients with epilepsy onset time within 0-6 months, 6-12 months, and over 12 months is shown.

The most common EEG disorder was multifocal and generalised epileptiform abnormalities. The EEG results were seen as normal in 8% of the patients, hypsarrhythmia in 8%, multifocal epileptiform changes in 20%, focal epileptiform and focal slowing in 20%, and generalised epileptiform discharges in 44%. The most frequently used anti-epileptic drugs were valproic acid, carbamazepine, vigabatrin, oxcarbazepine, lamotrigine, clobazam, and levetiracetamide. The age at onset of seizures was determined to be statistically significantly younger in the polytherapy group (5±4.75 months [range, 1-18 months]) than in the monotherapy group (8.0±16 months [range, 4-36 months]) (p=0.032) (Figure 2).

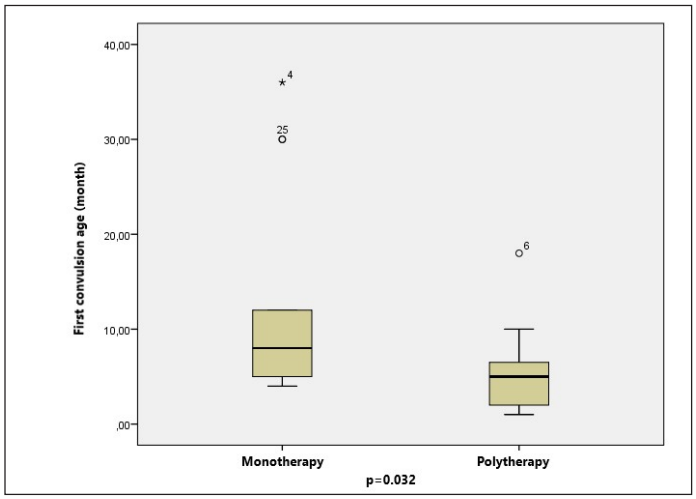

Figure 2. The epilepsy onset time was 8.0±16 (4-36) months in the monotherapy group and 5±4.75 (1-18) months in the polytherapy group. It was found that the onset time was statistically smaller in the polytherapy group compared to the monotherapy group (*p=0.032; Mann Whitney U-test).

The brain MRI findings were seen to be cortical tuber in 6 (22.2%) patients, subependymal nodule in 6 (22.2%), and the combination of subependymal nodule and cortical tuber in 15 (55.6%) (Figure 3). Hydrocephaly was present in 1 patient but there was no requirement for shunt during follow up. The groups (isolated cortical tuber, subependymal nodule and concurrent of subependymal nodule and cortical tuber) were found to be similar in respect of the presence of epilepsy ($p>0.05$).

Mental retardation was present in 16 (59%) patients and autism spectrum disorder in 5 (18.5%). When the skin examination findings were examined, there were seen to be hypopigmented patches in all the patients, facial angiofibroma in 6 and shagreen plaque in 1. Other system involvements were seen to be renal

involvement in 12 (44.4%) patients (10 renal angiomyolipoma, 2 renal cortical cyst), cardiac rhabdomyoma in 15 (55.5%), and eye involvement (retinal hamartoma) in 2. Of the total 27 patients, there were genetic results for 17. Of these, mutation in the TSC2 gene was determined in 14 (82.3%) and mutation in the TSC1 gene in 3 (17.7%). A family history of tuberosclerosis was present in 8 cases. The demographic data of the patients are shown in Table 1.

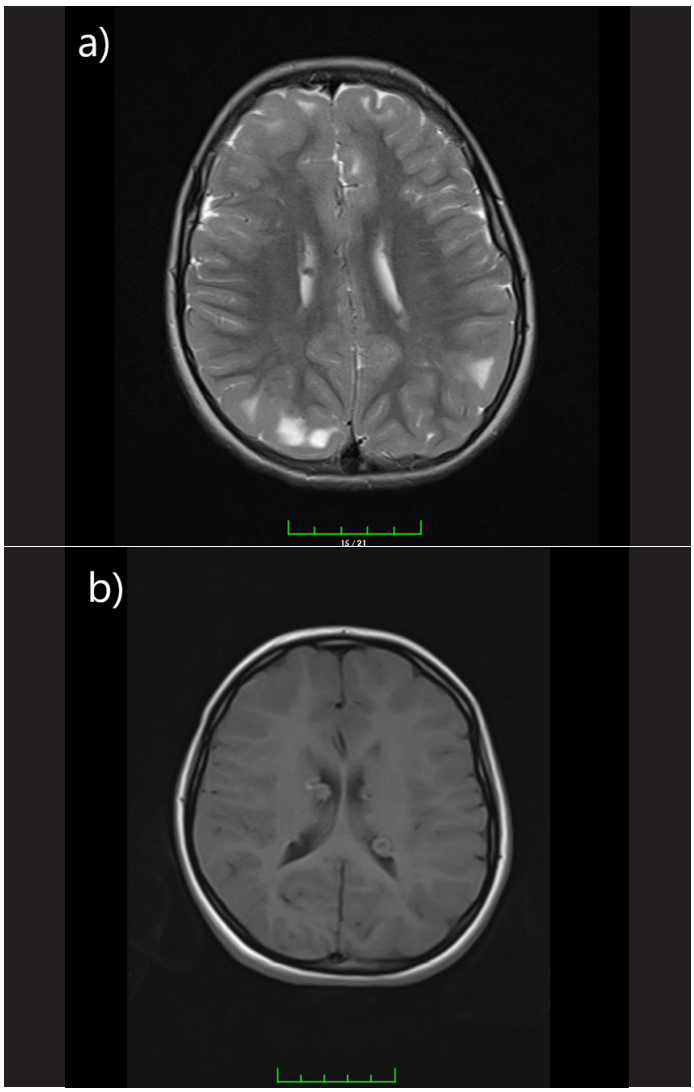

Figure 3. a) 8-year-old girl patient with tuberous sclerosis. Magnetic resonance imaging, T2 sequence examination, axial section. Subependymal nodules adjacent to the lateral ventricle and cortical tubers in the posterior regions are observed.

b) 15-year-old girl patient with tuberous sclerosis. Magnetic resonance imaging, T1 sequence examination, axial section. Subependymal nodules located adjacent to the lateral ventricle are observed.

Table 1. Demographic results of the study patients

Gender
Male (n:18)
Female (n:9)
First Presentation
Seizure (n:25)
Focal seizures (n:17)
Generalized seizures (n:8)
Other (n:2)
Antiepileptic Treatment
Monotherapy (n:14)
Polytherapy (n:11)
EEG Findings
Generalized epileptiform discharges (n:11)
Focal epileptiform and focal slowings (n:5)
Multifocal epileptiform changes (n:5)
Hypsarrhythmia (n:2)
Normal (n:2)
MRI Results
Cortical tubers (n:6)
Subependymal nodules (n:6)
Coexistence of subependymal nodules and cortical tubers (n:15)
Level of Cognitive Development
Mental retardation (n:16)
Autism spectrum disorder (n:5)
Normal (n:6)
Skin Examination
Hypopigmented spots (n:27)
Facial angiofibromas (n:6)
Shagreen patches (n:1)
Extracutaneous System Involvement
Renal angiomyolipoma (n:10)
Renal cortical cyst (n:2)
Cardiac rhabdomyoma (n:15)
Retinal hamartoma (n:2)
Genetic Results (n:17)
Mutation in TSC2 gene (n:14)
Mutation in TSC1 gene (n:3)
Familial History
History of familial tuberous sclerosis (n:8)

DISCUSSION

Tuberosclerosis complex is a neurocutaneous, multi-systemic disease, which has different manifestations by affectng several organs. The central nervous system is one of the most commonly affected body parts in tuberosclerosis. Epilepsy is extremely common in tuberosclerosis patients and neurocognitive functions are negatively affected as a result of recurrent seizures

[11]. In the current study of a group of tuberosclerosis patients, the majority of whom had epilepsy, the age at onset of seizures, seizure type, the drugs used, the seizure course, and the effect on cognitive functions were evaluated. The study results demonstrated that early onset of seizures resulted in greater resistance to anti-epileptic drugs.

Epilepsy is the most frequently seen neurological finding, at the rate of 80-90%, in tuberosclerosis patients [4]. In a study by Incecik et al., 89.4% of the patients presented because of seizure, and in the current study the reason for first presentation was seizure in 92.5% of the patients [11]. Seizures starting in the first 6 months of life have been shown to lead to neurocognitive delay and increased frequency of autism coexistence are seen in epilepsy patients [12]. There has been reported to be mental or cognitive retardation in 75% of tubersclerosis patients with resistant epilepsy [13]. Consistent with the lierature, it was seen in the current study that epilepsy started within the first 6 months of life in 55.5% of patients, and mental retardation was present in 75% of these patients.

In patients with tuberosclerosis and epilepsy, the seizures are known to generally have an early onset and are more often in the form of focal seizures and infantile spasm [14]. Most of the seizures in the current study had early onset and 68 % of patients experienced focal seizures and infantile spasms. The patients with earlier onset of epilepsy were also seen to need polytherapy because of clinical resistance.

The most specific test for imaging of central nervous system (CNS) involvement in tuberosclerosis is MRI. Lesions showing involvement are seen as hyperintense on T2-weighted slices in adult patients, whereas in young children, this hyperintensity may not be seen in which case T1-weighted sequences should be examined. Cortical tubers which are malformations of cortical development may be involved anywhere from the cortex up to the white matter [15]. Epilepsy, autism, or other symptoms can be seen associated with the site of involvement of tubers. Cortical tubers and subependymal nodules, which have a more benign course, are observed in the vast majority of patients with tuberosclerosis [8]. In the current study, cortical tuber and subependymal nodule were present in 55.6% of the patients. In addition cortical tuber only was present in 22.2% of patients and subependymal nodule only in the other 22.2%. A previous study reported that cortical tubers could be seen at the rate of 90% and subependymal nodules at 80%, but in that study, the rate of combination seen was not stated [16]. Giant cell astrocytoma and white matter abnormalities are more rarely seen CNS abnormalities. No giant cell astrocytoma was observed in any of the current study patients. The association between cortical tuber and epilepsy and the epileptogenesis mechanism are matters of debate in literature and there are conflicting views [17, 18]. In the current study, the cortical tuber and subependymal nodule groups were seen to be similar in respect of the presence of epilepsy. These pathological structures were not seen to be different in respect of epileptogenesis.

There has been reported to be accompanying mental retardation in 50-55% and autism spectrum disorder in 20-50% of tuberosclerosis patients [18, 19]. In the current study, mental retardation was present in 59% of the patients and autism spectrum disorder in 18.5%.

Renal involvement is the second most frequently involved system in tuberosclerosis after the CNS, with renal angiomyolipoma constituting 80% of renal involvement and renal cysts 20% [20]. In the current study, renal involvement was determined in 44.4% of the patients. Consistent with the literature, angiomyolipoma was present in 83% of the current study patients, and cortical cyst in 17%.

Cardiac rhabdomyoma constitutes 45% of primary heart tumours in children, and this is the most common form of heart tumour in childhood [21]. Moreover, 70-90% of children diagnosed with cardiac rhabdomyoma are diagnosed with tuberosclerosis over time [22]. Although cardiac rhabdomyoma are histologically benign tumours, depending on the localisation and diagnosis in the neonatal period, they can occasionally lead to arrhythmia, ventriculomegaly and heart failure [23]. Cardiac rhabdomyoma was present in 55.5% of the current study patients, but no cardiac dysfunction was observed in any patient during follow-up.

Although this study is of value in respect of presenting the long-term follow-up of a series of cases with tuberosclerosis, which is an uncommon disease, there were also some limitations. In addition to the inherent limitation of the retrospective design of the study, as the majority of the patient group had epilepsy, the relationship with other findings (the presence of cortical tuber, mental retardation) could not be evaluated in the absence of epilepsy. A further limitation was that the effect of tuberosclerosis genetics on other parameters could not be evaluated as only 17 patients had genetic analysis results and there were very few

patients (n:3) with TSC1 gene mutation.

CONCLUSION

The results of this study demonstrated that epilepsy with early onset in tuberosclerosis patients could have a resistant course and there may be a need for polytherapy. There may also be neuropsychiatric retardation in these patients. However, the clinical status of epilepsy in tuberosclerosis was similar in both the cortical tuber and subependymal nodule groups.

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Original Research

Association Between the Success of Bariatric Surgery and Personality Traits

Okan İmre[1], Şükrü S. Toprak[2]

[1] Karamanoglu Mehmetbey University Faculty of Medicine, Department of Psychiatry, Karaman, Turkey
[2] Karamanoglu Mehmetbey University Faculty of Medicine, Department of General Surgery, Karaman, Turkey

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Correspondence
Okan İmre, M.D.
Address: Karamanoglu Mehmetbey University Medicine Faculty, Department of Psychiatry, Karaman, Turkey
e-mail: okanimre@kmu.edu.tr

ABSTRACT

Objective: Acceptable preoperative psychosocial indicators of weight loss after obesity surgery in morbidly obese(MO) patients are still unknown. In this study, the association between personality traits, multidimensional perceived social support, and the percentage of excess weight loss (EWL) following obesity surgery was researched in MO patients.

Methods: Participants in this prospective study were recruited from MO patients who applied to the hospital's obesity unit between July 2021 and June 2022. The study comprised 84 MO individuals. The Temperament and Personality Inventory (TCI) was used to evaluate the personality traits of the MO. Perceived social support was measured using the multidimensional perceived social support scale. The percentage of weight loss after obesity surgery was compared with personality traits and perceived social support scores.

Results: The mean age of the patients who were MO was 36.7 ±8.7 years. There were 22 men (25.3%) and 62 women (74.7%). The mean preoperative BMI was 46.2 ±63. The perceived social support score was 68.0±16.4. A univariate analysis found a positive relationship between 6 months and one year's EWL and Self-Transcendence, a TCI subcategory (p=0.011,p=0.023).

Conclusion: Obesity treatment is a complex situation that requires a multidisciplinary approach. Given the potential physiological and psychological consequences of obesity surgery, it is critical to uncover psychological predictive factors such as personality traits that boost the success of obesity surgery and are connected with weight loss. As a result, knowing the individuals who self-transcendence before obesity surgery may be useful in predicting the success of obesity surgery and planning treatment. This requires large-scale research.

Keywords: Obesity surgery; Personality; Self-transcendence

INTRODUCTION

Obesity is a chronic condition that causes a number of medical problems. Morbid obesity (MO) is defined as obesity that reduces lifespan and can have serious consequences depending on the risks it poses. For the treatment of obesity, there are numerous non-pharmacological options. One of the most effective non-pharmacological treatments for MO is obesitysurgery. Patients who have a BMI of at least 40, a BMI of 35 to 40 who have tried n dietary therapy but failed, and certain specific medical comorbidities should consider having obesitysurgery. Weight loss following obesitysurgery has been shown to reduce some obesity-related problems such as diabetes, and hypertension [1]. However, there are discrepancies in the outcomes of obesitysurgery for patients who are MO. Some people have difficulty losing weight after surgery. Some of them began to put on the weight they lost after the operation in the sixth month

[2]. It has been noted in studies on the variations in long-term outcomes after obesitysurgery that this circumstance is related to psychological variables [3]. It is crucial to be aware of these psychosocial aspects of weight loss, given the risk and expense of the procedure. Additionally, if these psychosocial characteristics are found, they can be used to help choose MO individuals for surgery and create follow-up strategies for people who are less likely to lose weight. Numerous studies on the causes of weight gain or loss after obesitysurgery have been published in the literature. An association between preoperative problematic eating and postoperative weight gain was discovered in a study [4]. In another study, it was revealed that various behaviors, such as non-compliance with treatment programs, were related to decreased weight reduction after obesitysurgery [5].

Recent research has concentrated on the association between weight loss following obesitysurgery and personality traits and social support. In the literature, investigations undertaken for this aim have discovered conflicting results between a certain personality attribute and the extent of post-operative weight loss [6,7]. While there is a body of literature on the topic, the relationship between personality traits and the outcomes of obesity surgery remains inconclusive due to conflicting findings. Some studies suggest a potential positive association between specific personality traits, such as self-discipline and motivation, and improved surgical outcomes. However, the mechanisms underlying this relationship and the consistency of these results require further investigation and clarification through rigorous research.

There are few studies examining the link between perceived social support and post-surgical weight loss, despite the fact that the relationship between social support and weight loss has been extensively researched in the literature [8]. As opposed to objective social support, it has been suggested that subjectively felt multidimensional social support may be a better indicator of psychological adjustment [9]. In conclusion, acceptable preoperative psychosocial indicators of weight loss after obesitysurgery in MO patients are still unknown. In this study, the association between personality factors, multidimensional perceived social support, and the percentage of excess weight loss (EWL) following obesitysurgery was researched in MO patients.

Main Points;

- Our findings suggest that there is a relationship between personality traits and the success of bariatric surgery.
- Self-transcendent individuals lost more weight after bariatric surgery.
- There was no association revealed between the temperament subscales and bariatric surgery success.

MATERIALS AND METHODS

Participants in this prospective study were recruited from MO patients who applied to hospital's obesity unit between July 2021 and June 2022. A committee of general surgery specialists, endocrine specialists, dietitians, and psychiatrists selects patients for surgery in the obesity unit.

The study comprised 84 MO individuals. Patients who were deemed unfit for surgery were referred to non-surgical treatment and were thus excluded from this study. The study excluded ten respondents because they refused to participate and three people because they filled out the scales improperly. Obese subjects aged 18–65 years with a BMI 40 kg/m2 were included in the study. The aim of the study was explained to the participants, and their permission was obtained.First of all, the sociodemographic data of the individuals and their preoperative weight were recorded. Second, the TCI was used to evaluate the personality traits of the MO. Finally perceived social support was measured using the multidimensional perceived social support scale.

Those who accepted the study and had obesitysurgery(Roux-en-Y gastric bypass) were tracked prospectively for one year beginning in July 2021. Weights were taken three, six, and twelve months after the operation. The percentage of excess weight loss (%EWL) was calculated. EWL was calculated by subtracting the preoperative weight from the postoperative weight, dividing the result by the preoperative weight, and multiplying by 100 [10]. The percentage of weight reduction was compared with personality attributes and perceived social support scores.

Temperament and Personality Inventory(TCI)

TCI stands for TCI. TCI is a 240-item self-assessment scale established by Cloninger (1987) to measure temperament and character characteristics based on Psychobiological Personality Theory [11]. It consists of four temperaments: novelty seeking (NS), harm avoidance(HA), reward dependency (RD), and persistence (P), as well as three personality sub-dimensions: self-

directedness (SD), cooperativeness (C)and self-transcendence (ST). The Temperament character inventory in Turkish was employed in the study. In a study on the mean (M) and standard deviation (SD) of TCI scales and subscales in Turkish population subjects, NS=18.5±5.00, HA= 6.8± 6.4, RD=14.1± 3.2, P =4.8 ±1.9, SD=29.1 ± 6.2, C= 29.4 ± 5.9 and ST= 18.6 ± 5.4 results were obtained [12].

The Multidimensional Scale of Perceived Social Support (MSPSS)

The belief that one can get help when needed is characterized as perceived social support. It's a seven-point Likert scale. Developed by Zimet et al. it is made up of three sub-dimensions: the family support dimension, the friend support dimension, and the special human support dimension, totaling 12 items [13]. The study made use of the Turkish version [14].

Statistical Analysis

The variables preoperatively described above were subjected to descriptive statistics. Data analysis for testing hypotheses was always done at the end of the study. First, a series of univariate analyses were carried out to examine the connection between the pertinent preoperative factors and the EWL at each endpoint. For variables that were continuous, Pearson correlation was applied. Following examination of the sample's normality distribution, t-tests for independent samples and ANOVAs were applied to categorical variables. The data were analyzed using SPSS software (v 22.0; SPSS Inc., Chicago, IL).

RESULTS

The mean age of the patients who were MO was 36.7 ±8.7 years. There were 22 men (25.3%) and 62 women (74.7%). The mean preoperative BMI was 46.2 ±63. The perceived social support score was 68.0±16.4. TCI scores of MO individuals were similar to those of the healthy Turkish population (Table1).

Table 2 shows the univariate analysis, which demonstrated a positive connection between 6 months and one year's EWL and preoperative BMI(p=0.032, p=0.002). EWL was found to be higher in unmarried MO patients at three months (p=0.010). Furthermore, a negative connection was discovered between three months EWL and the age of Obesity Onset. A univariate analysis found a positive relationship between 6 months and oneyear's EWL and Self-Transcendence, a TCI subcategory(p=0.011,p=0.023) (Table 2).

Table 1. Baseline features of the sample of 84 patients who have undergone Roux-en-Y gastric bypass

	Total (n=84)
Age (years)—mean (SD)	36.7 (±8.7)
Gender—n (%)	
Male	22 (25.3)
Female	62 (74.7)
Marital Status—n (%)	
Single	14 (16.9)
Married	63 (75.9)
Wife passed away	1 (0.01)
Divorced	6 (7.2)
Preoperative BMI —mean (SD)	46.2 (±6.3)
Age of onset of obesity —mean (SD)	16.8 (±8.4)
Perceived social support —mean (SD)	68.0 (±16.4)
Temperament and Character Inventory —mean (SD)	
NS—mean (SD)	17.3 (±5.1)
HA —mean (SD)	17.8 (±6.4)
RD —mean (SD)	13.0 (±3.2)
P —mean (SD)	4.6 (±2.0)
SD* —mean (SD)	26.0 (±6.9)
C —mean (SD)	28.9 (±6.9)
ST —mean (SD)	21.3 (±5.9)

TCI; Temperament and Character Inventory, HA; harm avoidance, NS; novelty seeking, RD; reward dependence, P; persistence, SD*; self-directedness, C; cooperativeness, ST; self-transcendence

DISCUSSION

In this study, the association between personality and the success of obesitysurgery in MO patients was studied. In our study, a positive link was discovered between %EWL at 6 months and 1 year following obesity surgery and Self-Transcendence(ST), one of the Temperament and Character Inventory (TCI) subcategories.

Temperament and character are two sub-dimensions of personality. Temperament is a genetically determined characteristic of personality. The side learned through societal interaction is character. Temperament is inherited and does not alter. Character is the dimension of personality learned through social interaction. Depending on the environment, this may alter over time [15]. There was no correlation between the percentage of weight loss following obesitysurgery and temperament sub-dimensions in our study. Only one of the character sub-

Table 2. Association between %EWL and baseline variables across the endpoints of patients who have undergone Roux-en-Y gastric bypass

	3-month %EWL		6-month %EWL		1-year %EWL	
	(n=84)	p value	(n=84)	p value	(n=84)	p value
Preoperative BMI[a]	0.075	0.508	0.257	0.032**	0.367	0.002*
Age[a]	-0.181	0.108	-0.190	0.115	-0.079	0.519
Gender[b]		0.206		0.712		0.087
Male	14.1 (±5.4)		25.8(±6.0)		37.7(±4.8)	
Female	15.1(±4.3)		23.9(±6.4)		33.8(±8.3)	
Marital Status[c]		0.010** (Group1>Group2)		0.114		0.136
Single(Group 1)	17.1(±3.4)		25.6(±6.0)		35.3(±6.7)	
Married(Group 2)	14.6(±4.4)		23.8(±5.7)		33.9(±7.3)	
Divorced (Group 3)	15.2(±5.9)		30.1(±12.6)		43.1(±16.4)	
Age of Onset of Obesity[a]	-.254	0.023*	-0.162	0.180	-0.101	0.410
Perceived social support[a]	-0.052	0.649	-0.061	0.618	0.117	0.338
Temperament and Character Inventory —mean (SD)						
NS [a]	-0.065	0.565	0.084	0.490	-0.054	0.660
HA [a]	-0.035	0.756	-0.105	0.389	-0.209	0.085
RD [a]	0.097	0.391	0.056	0.647	-0.057	0.642
P [a]	0.162	0.152	0.177	0.143	0.085	0.486
SD* [a]	0.005	0.963	-0.041	0.738	-0.072	0.558
C[a]	0.109	0.337	0.128	0.290	0.003	0.982
ST [a]	0.006	0.958	0.302	0.011**	0.273	0.023**

*p<0.005, **p<0.05, [a]Pearson's correlation, [b]T test for independent samples, [c]ANOVA
TCI; Temperament and Character Inventory, HA; harm avoidance, NS; novelty seeking, RD; reward dependence, P; persistence, SD*; self-directedness, C; cooperativeness., ST; self-transcendence

dimensions, Self-Transcendence, showed a positive association. Self-transcendence is the attempt to exceed one's own potential and attain gains greater than oneself. Beyond himself, it is the individual's efforts to benefit the environment and social life that, in self-transcendence, the individual attempts to solve not just his own difficulties but also the issues of others [16]. There is no evidence in the literature that there is a link between self-transcendence and weight loss following obesitysurgery. This finding may contribute to the literature for new research.

The role of personality traits as predictors of obesitysurgery outcome is still uncertain [17]. The findings of the few studies available are inconsistent. Some research revealed no association between personality traits and the outcome of weight loss [18-22]. A few studies on temperament sub-dimensions and postoperative weight loss were discovered after a literature search. According to certain studies, there may be a link between weight loss after obesitysurgery and some sub-dimensions of personality traits. Novelty-seeking is a behavior that is motivated by fresh discoveries. A few studies have identified a link between higher novelty-seeking ratings and more weight loss [6, 7]. Persistence is defined as the state of remaining determined and constant in the face of adversity [15]. Low-persistence obese individuals have been observed to have fewer consistent lifestyle modifications required for weight loss after obesitysurgery; hence, lower Persistence scores are positively associated with reduced weight loss [6, 23]. In other words, those who scored better on persistence lost more weight. A small number of studies studying the association between character sub-dimensions and postoperative weight loss were reported in the literature. A small number of studies have found a link between increased cooperativeness and weight loss after

obesitysurgery. This was explained by the MO person with a high Cooperativeness score interacting with social groups similar to himself and seeking more social support [24]. Higher self-directedness scores were associated with greater short-

term weight loss in one study [25]. In our study, no relationship was found between novelty seeking, persistence, harm avoidance, and reward dependence, which are the temperament sub-dimensions of personality, and weight loss after obesitysurgery. There was also no relationship between the personality sub-dimensions of cooperativeness, self-directedness, and weight loss after obesitysurger. This may be connected to the small number of our patients. Despite the limited evidence in the literature, there seems to be an association between personality traits and the outcome of obesitysurgery [26, 27]. There is much research in the literature studying the association between obesitysurgery success and social support. In most of the investigations, it has been observed that social support groups have a favorable contribution [28, 29].

There are few studies investigating the relationship between perceived social support, which is defined as different from social support, and obesitysurgery success.

Perceived social support refers to how a person perceives social assistance. In our study, there was no correlation between weight loss after obesitysurgery and perceived social support. Only one study in the literature directly explored perceived social support and obesitysurgery success. In this study, a difference in perceived social support in MO people before and after obesitysurgery was studied, but no difference was identified. There was no link discovered in the same study between the perceived social support and the level of post-operative weight loss [30].

Our research has some limitations. Because psychological pre-assessment is required for the operation, MO people may have hidden their problems and made themselves appear better than they really are. Our sample size was limited. Finally, we followed MO patients for up to 12 months following obesitysurgery. Our understanding of the long-term implications is inadequate.

CONCLUSION

Obesity has an extensive variety of effects on the body's systems, including the endocrine, cardiovascular, respiratory, genitourinary, gastrointestinal, musculoskeletal, and skin systems. It is also a medical issue that must be addressed due to the detrimental consequences it has on the psychological condition. In this regard, treatment must take a multidisciplinary approach. Given the potential physiological and psychological consequences of obesitysurgery, it is critical to uncover psychological predictive factors such as personality traits that boost the success of obesitysurgery and are connected with weight loss. Despite contradicting findings, there appears to be a relationship between personality traits and the outcome of obesitysurgery. As a result, knowing the individuals who self-transcendence before obesitysurgery may be useful in predicting the success of obesitysurgery and planning treatment. Large-scale studies are needed for this.

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Original Research

Effects of COVID-19 Pandemic on Preschool and Primary School Aged Children: Qualitative Reports of Turkish Parents

Abdülkadir Aydın[1], Yıldız Büyükdereli Atadağ[2], Ahmet Öksüz[3], Hasan Apaydın[4], Erkut Etçioğlu[1], Muhammet Raşit Aydın[1]

[1] Department of Family Medicine, Faculty of Medicine, Sakarya University, Sakarya, Turkey
[2] Department of Family Medicine, Abdulkadir Yüksel State Hospital, Gaziantep, Turkey
[3] Department of Family Medicine, Mimar Sinan Family Health Center, Sivas, Turkey
[4] Department of Family Medicine, Faculty of Medicine, Maltepe University, Istanbul, Turkey

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Correspondence
Yıldız Büyükdereli Atadağ, MD
Address: Department of Family Medicine, Abdulkadir Yüksel State Hospital, Gaziantep, Turkey
E-mail: yildizatadag@gmail.com

ABSTRACT

Objective: COVID-19 pandemic may cause negative effects on children. Qualitative studies evaluating the effects of the pandemic on preschool and primary school aged children are limited in the literature. The aim was to evaluate the effects of COVID-19 on preschool and primary school children through the observations of their parents.

Methods: In-depth interviews were made with the participants using video conferencing method. Seventeen video conferencing interviews were conducted with parents who had children between 3 and 10 aged. With the permission of the participants, audio recording was obtained in all interviews, transcribed verbatim and checked. Thematic approach was used to analyze the data. Data were collected until saturated.

Results: Findings were summarized into three main categories. The first was "The changes in the affection conditions". It's observed in the interviews that children experienced changes in their affection conditions such as fear, anxiety and happiness. They also went through behavioral changes like aggression and shyness. The second theme was "The Distinction in Behavioral Features". Parents believed their children's dominant behavioral features became more distinct. The third theme was "The changes in the Communication Levels". While the communication with the family members increases or decrease according to various factors, the communication with the non-family members decreases for almost all of the children.

Conclusion: The effects that children are exposed to in the face of global events such as pandemics should be considered separately in addition to social planning. Each child should be evaluated within their own family and environment.

Keywords: Children, COVID-19, effects of pandemic, qualitative research

INTRODUCTION

Countries all across the world were forced to take a series of precautions to decrease interactions between people as part of the fight against the COVID-19 pandemic. Imposing lockdowns on specific age groups during differing time periods and closing various workplaces and schools were the primary forms of these precautions [1]. However, it has been observed that although

these precautions were successful as preventative measures, in the background, they created different problems [2,3].

The United Nations has stated that, regardless of age, children were among the groups most affected by the pandemic [4]. Besides its direct effects on children, the pandemic has had other adverse effects on them, depending on the possible psychological, social, and economicproblems their parents face [5].

The results of the studies that have investigated the effects of the pandemic process on children demonstrate that it has affected them psychologically, socially, and physically. One of the main effects mainly observed in children is changes in their affection conditions. In addition, it has been observed that the pandemic caused several other changes, including sleeping disorders, malnutrition, and problems caused by inactivity [6-8].

This study aims to multi dimensionally employ parental observations to assess the effects of the pandemic process on preschool children, who are at the beginning of their developmental period, and on primary school children. We believe that the results will elucidate the action plans, especially of policymakers and parents, for the current pandemic process and possible social traumas in the future.

MATERIALS AND METHODS

Research Design

The study used a qualitative research design to analyze the psychosocial effects of COVID-19 on preschool and primary school-aged children. In-depth interviews were conducted with the participants using video conferencing.

Study Subjects

Using a purposeful sampling method, we selected 17 parents with children between the ages of3 and 10. The sample size was decided according to data saturation. The interview process was terminated when no new themes emerged during the interviews with the participants. Data saturation was reached after 15 interviews, and two more parents were interviewed to verify the saturation.

Main Points;

- The pandemic has serious negative effects on children.
- Children's dominant features like shyness or aggression became much more distinctivein the pandemic period.
- Each child has experienced different changes in their communication level.

Interview Outline

A semi-structured questionnaire to be used in the interview was prepared with the aid of expertopinions and through preliminary testing after the relevant literature was reviewed. Participants' age, number and age of children, features of their place of residence, and household structure were obtained at the start of the interviews. The main interview questions posed to the participants were as follows:

1. Have you observed any behavioural changes in your child(ren) during the pandemic? Ifso, could you explain and describe them?
2. Have you observed any changes in your child(ren)'s habits and daily routines during thepandemic? Could you explain and describe them?
3. Have you observed any changes in your child(ren)'s communication with you or othersduring the pandemic?
4. Have you observed any situations different from the ones you've already described? To increase the depth of the interview discussions, the participants were posed the followingquestions:

- Could you please provide more information about this topic?
- Could you please explain that more?
- Could you give any examples of that?

Data Collection

After explaining the purpose and function of the study in detail to all the participants, verbal informed consent was obtained from them.

The interviews were conducted by video conferencing due to pandemic conditions. Theinterviews were carried out by the first author, who had received training in qualitative interview skills. With the permission of the participants, audio recordings were obtained in all interviews. The interviews took 15-40 minutes per person. The recordings were transcribed verbatim by the researchers within 24 hours of the interviews and were reviewed by the interviewers for accuracy.

Data Analysis

The researchers reviewed the texts several times independently to determine the important sentences and emphasized points in the interviews. The statements considered meaningful were summarized, and themes were created. Any conflicting opinions about the contents of the themes were discussed and resolved by the researchers.

Ethical approval for this study was received from the local ethics committee. (Approval date: March 22, 2021, Number: E.20141).

RESULTS

Seventeen parents were enrolled in the study. The characteristics of them and their families arelisted in Table 1.

There theme categories emerged from the analysis of the interviews. These themes and theirsub-themes are described in

Table 1. Characteristics of the participants' families

Parents*	Characteristics
P1	The mother is a 37 year old doctor. The father is a 42 year old lawyer. They have got 2 kids; an 8 year old girl and a 2 year old boy. They consider their income status well. They live in their own apartment in a housing estate. They have a part-time employee to help taking care of the children.
P2	The mother is a 32 year old teacher. The father is a 34 year old doctor. They have got a 3 year old son. They consider their income status well. They live in their own apartment.
P3	The mother is a 35 year old housewife. The father is a 40 year old accountant. They have 3 daughters; a 4 year old and 2 year old twins. They live in an apartment. They consider their income status as medium. Their grandmother helps them to take care of the children.
P4	The mother is a 40 year old housewife. The father is a shoeseller. They have 3 sons at the ages of 8, 10 and 13. They live in an apartment in a housing estate. They consider their income status as bad.
P5	The mother is a 35 year old nurse. The father is a 40 year old doctor. They have a 8 year old daughter and a 4 year old son. They live in their own apartment. They consider their income status well. The mother took an unpaid leave to take care of her children.
P6	The mother is a 37 year old housewife. The father is 44 years old. He Works in daily jobs. They have a 10 year old son. They live in a rented apartment. They consider their income status as bad.
P7	The mother is a 35 year old architect but she doesn't work. The father is self- employed in the software industry.They have 3 children ; an 8 year old girl and two boys at the ages of 6 and 3. They consider their income status well. They live in a detached house.
P8	The mother is a 40 year old housewife. The father is a 44 year old textile worker. This is the second marriage of both of them. They have 2 daughters at the ages of 6 and 3. The mother doesn't have any children from her first marriage. The father has a daughter who is married from her first marriage . They live in their own apartment. They consider their income status as bad.
P9	The mother is a 36 year old housewife. The father is a 38 year old computer engineer. They have twins; a boy and a girl at the age of 7. They consider their income status as medium. They live their own apartment in a housing estate.
P10	The mother is a 35 year old nurse. The father is a 36 year old academist. They have a 10 year old son and a 6 year old daughter. They live in their own apartment. They consider their income status well.
P11	The mother is a 40 year old housewife. The father is a 44 year old accountant. They have a 9 year old son and 7 year old daughter.
P12	The mother is a 36 year old housewife. The father is a 36 year old officer. They have 2 sons at the ages of 7 and 3.They live a rented apartment. They consider their income status as medium.
P13	The mother is a 38 year old housewife. The father is a 37 year old teacher. They have girl twins. They live in a detached house with their parents which belongs to them. They consider their income status as medium.
P14	The mother is a 34 year old housewife. The father ia a biologist. They have a 4 year old daughter. They live in a rented apartment. They consider their income status as medium.
P15	The mother is a 34 year old medical secretary. The father is a 38 year old shipper. They have a 6 year old son.They live in a rented apartment.They consider their income status as medium.
P16	The mother is a 30 year old housewife. The father is a tourism Professional. He's self-employed. They have 2 daughters at the ages of 5 and 3. They live in an apartment in a housing estate. They consider their income status as medium now. However, they think it was good before the pandemic. They have a full- time employee who helps taking care of the children.
P17	The mother is a 38 year old private company secretary. The father is a 42 year old estate agent. They have 3 children; a 9 year old girl and two boys at the ages of 7 and 2. They live in arented apartment in a housing estate. They consider their income status as bad. Their parents help them to take care of their children.

Table 2. Themes and sub-themes

Theme	Sub-theme
The changes in the affectionconditions	● fear ● anxiety ● happiness
The distinction in the behavioralfeatures	● shyness ● aggression
The changes in the communicationlevel	● increase and decrease in the family communication ● decrease in the communication with non- family members

Table 2.

Theme 1: The Changes in the Affection Conditions

It was learned in the interviews that children experienced changes in their affection conditions,such as fear, anxiety and happiness. They also went through behavioural changes that manifested as aggression or shyness. The participants stated that their children were especially afraid of and concerned about the possibility of being infected with the disease and the severe potential consequences of becoming ill from COVID-19.

P4: "The children are grown now, and they are aware of everything. We got sick, and my condition (the father's) was quite severe. That scared the kids a lot. It formed a fear of being infected with the disease again in the children. For instance, my older son is afraid he would react like me if he is infected again."
P9: "For instance, they are concerned about becoming infected if they go to school. Now, theyhave such fears in their lives. We always feel anxious when we go out, which we don't unless there is a necessity."

P11: "We became overprotective. That increased their fears. Our son didn't want to go to schoolwhen we told him the schools were opening. He didn't even want to go to the garden."

P17: "Two of my children go to school, but they are always worried. Especially my older son is aware of everything, and I can see the fear in his eyes when he goes to school."

Some of the parents also expressed that their children were scared and ran away when somebodyvisited them, something they never did before the pandemic.

A remarkable finding from the interviews is that some of the parents stated that their children were happier in this period. What these parents had in common was that their children had a sibling whom they could communicate with in the house. While not all of the parents who had more than one child shared this opinion, all of the single-child parents (P2, P6, P14, and P15) stated that their child was unhappy throughout the day.

P7: "Actually they are happy to be all together. Especially the little ones, who are even happierto have their older sisters with them all the time."
P9: "…That they are twins relieved both us and them. Despite their different genders, being peers made them share things. They became both siblings and friends. They are both happy at home and so are we."
P13: "I think in this period, communication with their peers is what they need the most. So, I think they are very lucky. They spend time together throughout the day and so they are happy."
P15: "… he doesn't go to school. We are both working. He spends time with his grandparents. But it is not enough unless they have a peer... that's why he always seems to be unhappy. My wife and I wished he had a sibling for the first time…"

Theme 2: Distinction in Behavioral Features

Parents indicated to see aggressive and shy attitudes in their children. The remarkable point ofthese expressions was that the parents believed their children's dominant behavioral features became more distinct.

P1: "Generally she is a shy girl but it became exaggerated during the pandemic."
P2: "…he became quite aggressive. He had some aggressive attitudes before but I think itimproved in this period."
P6: "Actually, I can't say he used to be a very calm boy but he felt suffocated in this period. Iam not sure if it is because of puberty but he became more angry, obstinate and aggressive."
P14: "He used to be shy around people before the pandemic but he became even more timid aswe hardly ever had company

during this period."

Theme 3: The Changes in the Communication Levels

It is detected in the interviews with the parents that there have been changes in the communication levels of the children. While the communication with the family members increases or decreases according to various factors, the communication with the non-family members decreases for almost all of the children.

It's acquired that the children whose communication with family members increase or decrease have a set of common domestic features. Parents who stated that there has been a decrease in their children's communication level also mentioned several factors to contribute to this change.Not having a sibling, that both parents are working and the increase in the time period spent on TV, phone, devices like computers are some of them which are frequently mentioned.

P2: "Not having a sibling to play with made him very lonely. He started to spend all his time on the iPad."

P6: "He was left alone… He watches cartoons on TV all the time, which is self-sufficient. If hehad a sibling, he would have someone to communicate with."

P15: "…Spending time with grandfather and grandmother started to get bored after a while because they did not have peers. If he had a sibling, this period would have gone better."

P17: "It was an advantage for us that two of our three children were close in age. I can say that they learned to spend time together and their communication increased. But in this case, the little one was left alone… The older ones also sometimes played with the younger ones."

There were parents who claimed their children's communication level increased as well as therewere some parents to say it was decreasing. They stated that the decrease in the communication with non-family members led to an increase in the communication particularly between siblingswho don't have a huge age gap.

DISCUSSION

The COVID-19 pandemic, which is one of the most important events of this century, has profoundly affected the entire world. The impacts of this global threat have gone far beyond physical health problems. The precautions related to and the natural course of the pandemic have affected individuals and society in many different ways, including psychologically, socially, physically, and economically. Children, who are at the beginning of their development, are especially sensitive to such effects. Imposing lockdowns and school closures on children asa precaution against the pandemic may have resulted in traumatic consequences as they have gone through serious psychological changes resulting from the interruptions to their routines and daily activities [9]. In light of these concerns, the aim of this study was to present the effectsof the pandemic on preschool and primary school children through their parents' observations.The interviews with parents showed that the children who were aware of the pandemic experienced the fear of infection and especially of death. As a result, they avoided going to school or meeting non-family members. However, some parents stated that their children were happier, despite these fears, as they spent more time with their families due to the COVID-19 precautions. One of the conspicuous observations of the parents was that the children's dominant characteristics, such as shyness and aggression, became much more distinctive during the pandemic period. Moreover, there was often an increase in communication between family members accompanied by a serious decrease in communication with non-family members. The most stunning finding was that having a sibling had a significant effect on these changes in children.

We determined that the children were nervous about becoming infected and the related negative consequences. Children heard about the effects of the pandemic from their families, on TV, and via social media. They witnessed the anxiety of their parents and tried to keep up with the changes in their daily lives. There were psychological changes in children as a result of suddenly starting to wear masks, switching to distance education, seeing their parents constantlywashing their hands and cleaning themselves when they came home before they took care of their children for fear of spreading the virus (and even avoiding physical contact with their children), and receiving news of the infections and deaths of people they knew. The fear of getting infected and the traumas of children who were infected negatively impacted children'spsychological states. It has been reported that children infected with or isolated because they might have COVID-19 sometimes developed fears of separation from their parents, being singled out, and being infected by an unknown disease. They were also likely to experience anxiety, acute stress, and adjustment disorders due to social isolation [10,11]. Moreover, school closures and separation from their parents may have caused them stress and anxiety [12–14]. Children may have had

difficulty avoiding physical and mental damage as they lack the skills to cope with the related stress and could not express their emotions like adults.

Jiao and et al. conducted a poll of the parents of 320 children between the ages of 3 and 18, which demonstrated that according to the parents, the children were afraid of asking questionsabout the pandemic and health-related issues. In addition, they had problems such as sleeping disorders and nightmares, anorexia, physical disorders, attention deficit issues, and engaging in sympathy-seeking behaviors. To overcome these problems, Chinese doctors suggested parents increase their communication with their children by playing collaborative games, doing activities, and singing together to help alleviate feelings of loneliness [15]. Another similar study from India that examined the effects of the pandemic and isolation on children and adults showed that 69% of the children had feelings of anxiety, 66% felt desperate, and 61% were scared [11].

Having a sibling particularly affected the psychological states of children during this period. In our study, it was observed that siblings who spent more time together improved their communication and positive interactions. While not all the parents with more than one child shared this view, all the single-child parents noted that their child was unhappy during the day. A study by Christner et al. showed that during the pandemic, only children had more emotional and hyperactivity problems while children with siblings developed more behavioral problems [16]. In a study in China, a survey of 11681 children showed that while 35.2% of only children and 38.8% of children with siblings showed signs of depression, 20.5% of only children and 24.7% of those with siblings showed symptoms of anxiety [17]. Given these findings, Dunton et al. stated that because of the lack of access to sports and activities, older children should be encouraged to engage in free and unstructured physical activities by playing games with youngchildren while also social distancing and wearing masks [18]. We also suggest parents spend more time with their children through daily activities, such as reading to their children and doing sports, games, and handcrafts at home.

Parents emphasized that during this period, acts of violence and abstention became more distinct in their children. For parents whose children already engaged in aggression and abstention, those behaviors became more severe. In accordance with our study, Imran et al. stated that issues such as having trouble with siblings, unhappiness, aggression, and social avoidance were observed during COVID-19 [13]. In the same study, parents also stated that they realized their toddlers and pre-school children were more anxious, and when they tried to focus and join in games, they became more aggressive. Additionally, negative parental attitudes, such as criticism and violence against children in the family, increased the likelihood of children's behavioral problems, such as disobedience and aggression [19]. A study in Israel showed that during the Covid -19 pandemic 55.8% of children preferred to sleep in their parents' bed and 45% of them mentioned about fears which they did not have before. It is pointed out that most of the children became more angry and 41.4% of them had difficulty in sleeping [20]. United Nations Children's Fund explains the effects of the COVID-19 pandemic on children as the effects of the infection of themselves and other family members, the socio- economic effects of the virus, the effects of the precautions on children and interruption of the steps taken to maintain and develop the rights of children [21]. And they made a number of recommendations on how to treat children. First of all, encouraging children to talk frankly about the pandemic and isolation by maintaining the conversation in the limits of the children'sknowledge on the subject is suggested. For young children who don't have enough informationon the subject it is better to talk about basic hygienic measures and simple precautions. Duringthese conversations it is crucial to be honest and not hide the truth. Children may perceive the news they hear from TVs and social media in a different way and they might think they are in danger. For this reason, they should be reassured that they are safe and they should be taught how to protect themselves and their friends in accordance with their age group. UNICEF also warns the parents to be calm and suggests them to show diligence not to reflect their own fears and reservations to their children [21].

Interviews with the parents showed that there has been changes in the communication level oftheir children. While there has been an increase in communication with family members, nearly no communication with non-family members was detected. Parents stated that having no siblings, having working parents and the increase in the time they spent on TV, phone and computer led to a decrease in their children's communication level. Parents who claim their children to become more communicative stated that their children communicated more with their siblings who are at similar ages. Healthy communication with children and good parentingare key points to relieve the children during long-term isolations [22]. In similar articles, it is pointed out that the children spend too much screen time [20]. There is not a sufficient

amountof articles on children's communication factor during the pandemic. In our study, we are determined that siblings with less age gap increased their communication which led to their happiness. These results should be examined through more studies. This study has restrictions as the findings about children are achieved through the parents' observations and small samplings. Moreover, it is possible that the pandemic process may have affected the parents' point of views and their perception of the children's attitudes. Even more,this destructive process may have caused the parents to be more judgmental towards their children. The interviews with the parents were conducted by considering all these possible effects and we avoided being directive.

CONCLUSION

As a result, it is seen that the pandemic has serious negative effects on children. In this case, there are characteristics, such as having siblings in the family, which reduce or favour these effects. The effects that children, who are the guarantee of our future, are exposed to in the face of global events such as pandemics should be considered separately in addition to social planning. Each child should be evaluated within their own family and environment.

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Ethical Approval: Sakarya University Faculty of Medicine Clinical Research Ethics Committee approval was obtained for this study on March 22, 2021, Number: E.20141

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Original Research

Comparison of the Effectiveness of Pulse Radiofrequency in the Treatment of Suprascapular Nerve in Chronic Shoulder Pain

Çağatay Küçükbingöz[1], Ayşe Bahşi[2], Tamer Bayram[2], Fidan Marufoğlu[2], Hayri T. Özbek[2]

[1] Department of Anesthesiology&Reanimation, Ministry of Health Adana City Training & Research Hospital, Discipline of Pain Medicine, Adana, Turkey
[2] Department of Anesthesiology&Reanimation, Çukurova University Faculty of Medicine, Division of Pain Medicine, Adana, Turkey

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Correspondence
Cağatay Küçükbingöz
Address: Ministry of Health Adana City Training & Research Hospital, Department of Anesthesiology and Reanimation- Algology Clinic, Dr. Mithat Özsan Bulvarı Kışla Mah. 4522 Sok. No:1 Yüreğir, Adana / Turkey
E-mail: ckbingoz.md@gmail.com

ABSTRACT

Objectives: To investigate the effects of various durations of pulsed radiofrequency (PRF) application on pain and functional limitation in the short term in patients suffering from chronic shoulder pain.

Methods: Eighty three patients, 50 women (60.2%) and 33 men (39.8%) were included in the study. Ultrasound-guided PRF treatment of the suprascapular nerve was performed for 8 min in 44 (53.1%) and 10 min in 39 (46.9%) patients. The pain intensity of the patients was evaluated using the visual analog scale (VAS). The Shoulder Pain and Disability Index (SPADI) was utilized to define shoulder function and pain. VAS and SPADI measurements before and four weeks after treatment were recorded.

Results: The VAS and SPADI scores showed a significant improvement in both treatment groups ($P < 0.05$); however, no significant difference was observed between the groups.

Conclusion: Therefore, PRF of the suprascapular nerve is a beneficial treatment method in patients suffering from chronic shoulder pain; furthermore, the duration of PRF treatment of 8 or 10 minutes does not affect the effectiveness of the treatment.

Keywords: chronic shoulder pain, suprascapular nerve, pulsed radiofrequency

INTRODUCTION

Shoulder pain is a widespread source of pain after back and knee pain in musculoskeletal diseases [1]. The prevalence of shoulder pain in the general population is approximately 16%, and it occurs more often in women [2]. Its prevalence increases with age and is more common after the age of 65 years [2, 3]. Considering the high prevalence rate, functional limitation, and high chronicity, shoulder pain is not only substantial for patients' life quality but also for resource management in health [4]. Chronic shoulder pain has many different causes including rotator cuff disease, impingement syndrome, acromioclavicular osteoarthritis, adhesive capsulitis and glenohumeral osteoarthritis [5, 6].

In patients suffering from shoulder pain, activity modification and analgesic drugs are often administered in the first stage. If no improvement is observed despite these treatments, physical therapy applications can be attempted. However, in the absence of any improvement, clinicians may utilize the administration of ultrasound (US) or fluoroscopy-guided injection of local anesthetics and steroids into the symptomatic joint or tissue, including glenohumeral, acromioclavicular joint, and subacromial space. Surgical approaches may be considered in cases that do not benefit from conservative treatment [6, 7].

The suprascapular nerve (SSN) contributes to the sensory innervation of the glenohumeral and acromioclavicular joints and the motor innervation of the supraspinatus and infraspinatus muscles [8]. SSN block can subsequently increase the range of motion and decrease shoulder pain in different chronic shoulder pain syndromes [9-12]. If the duration of action of local anesthetics in the peripheral nerve block is insufficient, pulsed radiofrequency (PRF) lesioning can be exploited for long-dated pain palliation accompanied by positive results [13]. PRF of the SSN was reported to be as well as, if not better than, steroid and local anesthetic applications [14].

PRF is believed to have a neuromodulator effect rather than neurodestructive effect which is particularly advantageous during treatment [15]. PRF is a non-neurolytic lesioning technique for pain palliation, and no proof of neural damage has been reported after PRF administration [13, 16]. Erdine et al. [17] reported that PRF treatment caused microscopic detriment to the internal ultrastructural components of axons, which leads to the deterioration and disorganization of membrane and mitochondrial morphology and microfilaments and microtubules.

There is no consensus in the literature concerning the duration and parameters of PRF treatment [18, 19]. In clinical practice, the optimal exposure time of PRF remains obscure and the duration of exposure is selected based on the experience of the clinician [19, 20]. The number of studies examining the effect of various duration of PRF application on the recovery and functionality of patients is limited. Therefore, performing a study on this subject may provide valuable insights.

The aim of this study was to investigate the effects of various duration of PRF application on pain and functional limitation in the short term in patients suffering from chronic shoulder pain.

Main Points;

- Chronic shoulder pain is a common cause of musculoskeletal pain.
- Suprascapular nerve Pulsed Radiofrequency treatment helps alleviate pain and improve function.
- The duration of PRF treatment of suprascapular nerve of 8 or 10 minutes does not affect the effectiveness of the treatment.

MATERIALS AND METHODS

Patients

Patients who presented with shoulder pain due to adhesive capsulitis, supraspinatus tendinitis, shoulder impingement syndrome, and/or subacromial bursitis diagnosed at the Algology Department of Çukurova University between 2019 and 2021, and who have had shoulder pain complaints for at least three months, were included in the study, and pulsed radiofrequency treatment of the suprascapular nerve was performed under ultrasound guidance. Prior to the study, approval was obtained from Çukurova University Clinical Research Ethics Committee (06.01.2023-no: 129). After ethics committee approval, patients' medical record was retrospectively analyzed. Written informed consent was obtained from all patients before the procedure. Data were procured from patient files and follow-up forms. Cases with incomplete data in the files, individuals who did not undergo shoulder magnetic resonance imaging before treatment, patients with visual analog scale (VAS) and Shoulder Pain and Disability Index (SPADI) data deficient, and individuals with complications leading to premature termination of the procedure were excluded from the study.

The pain intensity of the patients was assessed using the VAS. The SPADI, a 13-item scale, was utilized to evaluated shoulder function and pain. VAS and SPADI measurements before and four weeks after treatment were recorded.

Procedure

All injections were administered in the operating room by experienced physicians using US-guided technique. The patient was positioned in a sitting position, intravenous access was established, and standard monitors (pulse oximetry, electrocardiogram, and noninvasive arterial pressure) were appropriately attached. The patient was premedicated with 2 mg intravenous midazolam bolus without affecting the patient's consciousness. The skin site was prepared and draped in a standard, sterile fashion, using a povidone iodine-based skin prep. The suprascapular notch and the insertion of the needle into the SSN monitored using US (Edge, Sonosite, Bothell, WA, USA) using a high-frequency linear probe (HFL50xp, 15-6 MHz) (Video 1, Figure 1). Skin anesthesia was accomplished by administering 1%, 1 cc lidocaine with a 25 G needle. Through an in-plane approach, a 22 G, a 10-cm long echogenic radiofrequency (RF) cannula having a 5-mm long active tip (EchoRF, St Jude Medical, Plymouth, MN, USA) was inserted into the suprascapular notch (Fig. 1 and Video 1). Appropriate

localization of the needle tip was confirmed under US. Sensory stimulation was subsequently implemented at 50 Hz at 0.5 V. Patients described paresthesia, tingling, and pain in the deltoid and upper arm region. The motor stimulation was then performed at 2 Hz at 1 V and twitches were observed in the shoulder girdle. After negative blood aspiration, 1 mL of 2% lidocaine was injected. Afterwards, 1 minute following the local anesthetic injection, the first group received a total of 480 seconds (8 minutes) of PRF with 4 cycles of 120 seconds each at 42°C, 45 V, 2 Hz frequency, and 20 ms wavelength. The second group was subjected to a total of 600 seconds (10 minutes) of PRF with 5 cycles of 120 seconds each at 42°C, 45 V, 2 Hz frequency, and 20 ms wavelength. After the PRF procedure, 8 mg dexamethasone (2 ml), 2 ml 0.5% bupivacaine, and 2 ml 1% lidocaine were mixed with 2 ml normal saline and administered to the patient at a total volume of 8 ml (Video 2). The treatment spreading through the tissues was visualized by US imaging. Patients were followed up for 1 hour in the postoperative care unit owing to possible complications.

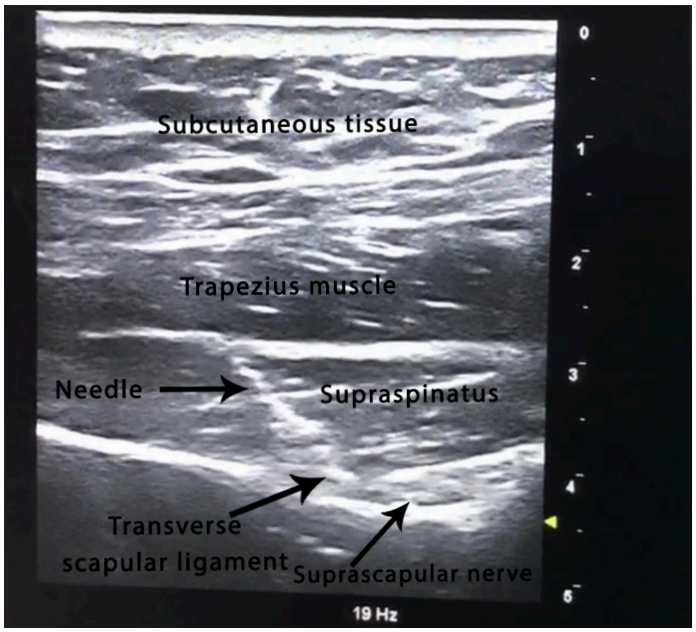
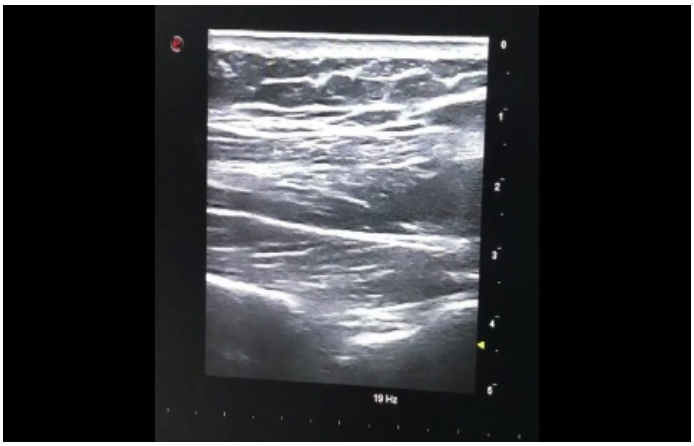
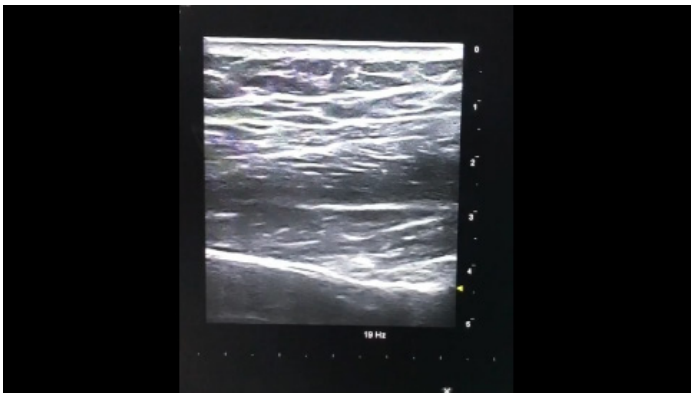


Figure 1. Anatomical structures observed in the intervention of the suprascapular nerve in ultrasound imaging.



Video 1. Demonstration of real-time pulse radiofrequency needle insertion into the suprascapular nerve under ultrasound guidance



Video 2. After the PRF procedure, administration of injection therapy and its spread under the transverse scapular ligament under ultrasound-guided

Statistical Analysis

SPSS 25.0 (Version 25.0, SPSS Inc., Chicago, IL, USA) package program was used for statistical analyses. Categorical measurements were summarized as numbers and percentages and continuous measurements as mean and standard deviation (median and range, where applicable). Student's t-test was used for intergroup comparison of normally distributed data. Paired samples t-test was used for comparing pre- and post-procedure measurements. $P < 0.05$ indicated statistical significance in all analyses.

RESULTS

In this study, 147 patients who had shoulder pain for at least three months and underwent US-guided SSN PRF treatment between 2019 and 2021 were included. According to the specified criteria, 64 cases were excluded. Of the remaining 83 patients, 50 were female (60.2%) and 33 were male (39.8%). The mean age was 58.57 ± 11.47 years (mean age for men and women, 60.45 ± 10.80 and 57.32 ± 11.83 years respectively). No significant intergroup difference was observed in terms of age and sex ($p = 0.225$) (Table 1).

Of the 83 patients included in the study, 44 (53.1%) underwent PRF to SSN for 8 min and 39 (46.9%) for 10 min. The 8- and 10-min treatment groups showed no differences in terms of pre-treatment VAS, pre-treatment SPADI, and symptom durations

(p = 0.898, 0.064, and 0.157, respectively) (Table 1). Comparison of the pre- and post-procedure VAS and SPADI values revealed significant differences. Changes in VAS and SPADI values before and after the procedure showed no significant intergroup differences (p = 0.387 and 0.831 for VAS and SPADI, respectively) (Table 2).

Table 1. Pre-procedure measurements

Parameter	8 min	10 min	p
Age	60.59 ± 9.68	56.28 ± 12.95	0.088
VAS	6.39 ± 0.87	6.36 ± 1.06	0.898
SPADI	59.54 ± 8.11	63.19 ± 9.62	0.064
Symptom Duration	7.14 ± 2.21	7.85 ± 2.32	0.157

Table 2. Comparison of pre- and post-procedure measurements

	n	Pre-Procedure	Post-Procedure	p
8 min VAS	44	6.39 ± 0.868	2.61 ± 1.19	0.001*
8 min SPADI	44	59.64 ± 8.10	23.09 ± 11.18	0.001*
10 min VAS	39	6.36 ± 1.06	2.85 ± 1.50	0.001*
10 min SPADI	39	63.19 ± 9.62	27.38 ± 13.85	0.001*
Total VAS	83	6.37 ± 0.96	2.72 ± 1.33	0.001*
Total SPADI	83	61.25 ± 9.98	25.11 ± 12.61	0.001*

*Significant difference

DISCUSSION

The SSN arises from the upper body of the brachial plexus at the junction of the ventral branches of the 5th and 6th cervical nerves and occasionally from the 4th cervical nerve; furthermore, the SSN comprises motor and sensory fibres [12, 21]. SSN has the greatest contribution in terms of overall shoulder innervation through its upper and lower articular branches [22]. Additionally, it provides motor innervation of the supraspinatus and infraspinatus muscles [8]. Therefore, when planning treatment, the motor fibres in the SSN that innervates the supraspinatus and infraspinatus should not be affected to preserve the existing motor function [23].

SSN blockade is known to be effective in the management of acute and chronic pain that may develop after trauma or surgery, independent of many etiologies. Although the efficacy of blockades with local anesthetics can be prolonged by adding steroids to the treatment, the duration of efficacy has not been sufficient in cases of chronic pain [24, 25]. Thus, several studies have emphasized that the use of the radiofrequency method in treatment is superior to the injection method in managing chronic shoulder pain [13, 14].

Radiofrequency therapy offers a cost-effective treatment modality for individuals suffering chronic and postoperative pain [26]. It is also a convenient alternative treatment for patients who cannot undergo surgical intervention [23, 26]. This therapeutic modality can be applied frequently in shoulder-related pain and has been reported to greatly contribute to recovery [11, 23, 26]. SSN PRF treatment helps alleviate pain and improve movement and function [10-12, 27]. This procedure is generally performed using US, among other guidance techniques [11, 12, 23, 27, 28]. US can provide an accurate visualization of the SSN [11].

Although the exact mechanism of radiofrequency treatment for chronic pain relief remains uncertain, the radiofrequency application was reported to diminish long-term pain by altering the expression of the c-fos gene in pain sensory neurons and producing a neuromodulator effect [29, 30]. Radiofrequency applications can be categorized into the following two treatment modalities: pulsed and conventional thermocoagulation. Since PRF provides neuromodulation without causing neural damage and without damaging the surrounding tissues, usage of PRF is recommended in nerves with both sensory and motor functions [11, 15, 19, 23, 31]. We preferred PRF application because the SSN has both sensory and motor branches. No consensus exists regarding the duration and parameters of PRF treatment [18, 19]. The optimal application time for PRF is uncertain and the application time is arbitrarily preferred in clinical procedures [19, 20]. PRF is predominantly executed for 2–8 min [19, 20, 30-34].

In the present study, PRF application on SSN for 8 or 10 min in patients suffering from chronic shoulder pain (rotator cuff, impingement syndrome, adhesive capsulitis) was found to be an efficient method in alleviating shoulder pain in a short period of 4 weeks. Jang et al. [35] noted that 4 min PRF treatment of SSN resulted in at least nine months of improvement in 11 patients with chronic intractable shoulder pain. Lüleci et al. [31] reported that PRF treatment of SSN applied for 8 min provided 6-month pain control in 45 of 57 patients (78.9%). Gurbet et al. [33] reported that the application of PRF for 2 min to the SSN in two cycles improved pain control and shoulder range of motion for three months in 8 patients with shoulder pain unresponsive to medical treatment or physiotherapy. Although there is not sufficient data in the literature that PRF treatment of SSN for 6 min can provide longer-term pain control than 4 min, it has been shown that antiallodynic activity increases when PRF time is increased from 2 minutes to 6 minutes [20]. This indicated that

PRF has a long-acting effect on nociceptive pain [27].

To investigate the effect of prolonged PRF exposure, Arakawa et al. [36] compared 6 and 12 min of PRF in rats with sciatic nerve lesions and found that the effects of PRF currents applied for 12 min were not significantly different from PRF applied for 6 min. Similarly, no significant intergroup difference was noted in the present study.

Similar to the studies conducted by Ergönenç et al. [27], Wu et al. [11], and Liliang et al. [13], a decrease in mean VAS and SPADI values was observed at follow-up. In the present study, mean VAS and SPADI values measured four weeks after the procedure were significantly lower than baseline measurements in both 8-and 10-min PRF groups. The decrease in the mean VAS and SPADI values of the patients was reported to be similar with 8 and 10 min of PRF application. Reportedly, neither duration of PRF administration was superior to the other on pain and functionality.

In patients suffering from shoulder pain, PRF therapy resulted in favorable clinical efficacy for at least 12 weeks [37]. US-guided PRF treatment of SSN is an effective treatment modality for managing chronic shoulder pain. In the present study, we performed US-guided PRF combined with steroid treatment on SSN in all our patients. The effects of the combination of PRF and a short-acting corticosteroid were shown to last up to 24 weeks [38].

PRF is a simple, minimally invasive treatment procedure that is predominantly well tolerated among older adults; however, it continues to have the potential risk of complications including bleeding, infection, nerve injury, and neuroma. The most important complication is the development of pneumothorax [35, 39]. This risk can be significantly minimized using US as observed in the present study. In addition, no complications or side effects were observed in our patients during the follow-up period.

Further randomized controlled trials with longer follow-up periods comparing the efficacy of PRF application duration on the SSN are required to fully clarify its role in the treatment of chronic shoulder pain.

Limitations

The retrospective study design, the absence of a control group, the relatively short follow-up period, and the small sample size were the limiting factors of our study.

CONCLUSION

Several studies in the literature have examined PRF treatment of the SSN; however, to the best of our knowledge, no definitive guideline exists on the algorithm of PRF treatment duration. However, despite its limitations, the results obtained in the present study were significant as they supported the small number of comparable articles in the literature and show that the duration of treatment does not have a visible effect on efficacy.

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Ethical Approval: This study was obtained from approval by Çukurova University Clinical Research Ethics Committee (06.01.2023-no: 129).

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Original Research

Computed Tomography Based Evaluation of the Anterior Group of the Paranasal Sinuses

Fulya Yaprak[1], Istemihan Coban[1], Orkun Sarioglu[2], Mehmet Asim Ozer[3], Figen Govsa[3]

[1] Department of Anatomy, Izmir Democracy University, Faculty of Medicine, İzmir, Turkey
[2] Department of Radiology, Dokuz Eylül University, Faculty of Medicine, İzmir, Turkey
[3] Department of Anatomy, Ege University, Faculty of Medicine, İzmir, Turkey

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Correspondence
Fulya Yaprak, MD, Lecturer
Address: Izmir Democracy University, Faculty of Medicine, Department of Anatomy
E-mail: fulyaprak@hotmail.com

ABSTRACT

Objective: The study aims to ascertain the prevalence of paranasal sinus variations among healthy adults in the Turkish population, as well as to analyze the symmetry of these variations.

Methods: The CTIs of 200 adult patients who did not have any trauma, carcinoma, tumor, surgery, or a condition that could affect the paranasal anatomy, such as chronic rhinosinusitis, were included. The prevalences of the Agger nasi cell (ANC), supraorbital ethmoid cell (SOEC), Haller's cell (HC), middle turbinate pneumatization, and frontal sinus (FS) agenesis variations in the adult Turkish population were revealed.

Results: Bilateral SOECs were found 38.5% of 200 patients, and at least 53% of patients had SOECs on one side. In 21.5% of instances, LCs were observed on both sides; in 35% of instances, they were observed on at least one side. ANCs were observed bilaterally in 68.5% of the total, the rate of patients with ANC on at least one side was 84.5%. The rate of bilaterality of the HC was 24%, it was observed at least one side in 43% of the cases. Bilateral concha bullosa (CB) were observed in 19% while CB variation on at least one side was 42%. Bilateral absence of the FS was found to be 8.5%, and unilateral absence was 2.5%.

Conclusion: The most common paranasal sinus variation was ANC, while the least was FS agenesis. Bilateral inheritance was found to be most prevalent in SOEC. The findings of our study hold significance for interventional procedures involving the paranasal region.

Keywords: Paranasal sinuses; Anatomic variations; Paranasal sinus diseases; Conchae nasales; Frontal sinuses

INTRODUCTION

Paranasal sinuses are a highly variable group of air-filled cells surrounding the nasal cavity. Radiological evaluation of the structures is a prerequisite for defining the location and involvement in several paranasal maladies and pre-operational treatment planning, such as endonasal endoscopic sinus surgery [1]. This variability may cause clinical findings that affect the quality of life and require surgical intervention [2]. The ability to perform interventions in the paranasal region with fewer complications has been facilitated by advances in radiological imaging options and surgical techniques, as well as a greater comprehension of regional anatomy [3]. The variations and complex three-dimensional structure of thin bone plates close to one another can be quite challenging for novices lacking anatomical knowledge, as well as experts familiar with the highly variable anatomy of the paranasal region [4]. Many

anatomical variations related to the paranasal sinuses have been reviewed before and besides posterior group sinonasal region anomalies (like sphenoidal sinus agenesis or sphenoethmoidal recess anomalies [5, 6] septum nasi deviations, frontal sinus agenesis, agger nasi cells (air cell located in the anterior part of the superior portion of the middle turbinate), concha bullosa (pneumatization of the middle turbinate), lamellar cells (aeration of the vertical lamella), Haller cells (aerial cell located in the inferior of the inferior orbital wall) and, supraorbital ethmoid cells (located in the superior part of orbital wall) are reported to be common variations [7] and genetics, environmental factors, age, gender and ethnicity are seen as the main determinants of these variations [8]. Although most of the variations with congenital features are coincidental, it is possible that the paranasal sinuses are affected or affect in a lesion involving the surrounding soft tissues [9]. Regional variations or anomalies should be studied in detail in order to investigate the effect of a disease involving the important soft tissues around the paranasal sinuses on the sinonasal region tissues [9, 10].

Studies in this area have mostly focused on the incidence of a certain variation or common clinical findings such as sinusitis [3-8]. Although these variations have been studied in studies conducted in Türkiye, the number of studies in which gender, age group and symmetry analysis has been done is very few [6, 10, 11].

Main Points;

- 38.5% of patients had bilateral supraorbital ethmoid cells (SOECs), and at least 53% had SOECs on one side.
- The most common paranasal sinus variation observed was agger nasi cell (ANC), while frontal sinus (FS) agenesis was the least common.
- Bilateral inheritance was most prevalent in supraorbital ethmoid cells (SOECs).
- 91.5% of the population had bilateral frontal sinuses, and 3.5% had frontal sinus agenesis on both sides.
- Lamellar cells (LCs) were present bilaterally in 21.5% and at least on one side in 33.5% of cases.
- Agger nasi cells (ANCs) were observed bilaterally in 68.5%, and at least one side had ANCs in 84.5% of cases.
- The findings have significance for interventional procedures involving the paranasal region and highlight the importance of radiological evaluation and pre-operational treatment planning.

The study aims to describe the anatomical formation of the paranasal sinus in individuals whose anterior sinonasal region is intact in the adult Turkish population and to reveal the frequency of these variations, age, gender, and symmetry analysis with retrospective assessment of CTI.

MATERIALS AND METHODS

This research involves human participants and ethical approve was taken from the Ethical Committee of Ege University under project number 20-7.1T/12.H.

Patients

Images obtained from two hundred patients who underwent CTI scans for various reasons (not paranasal sinus related) at University Hospital between June 2011 and January 2018 were evaluated retrospectively (mean age 46, range 18-70, 100 females, 100 males). The patients included in the study were not subjected to any trauma, carcinoma, tumor, surgery, or chronic rhinosinusitis that might alter paranasal sinus anatomy and under 18 years old. The patients were divided into two groups according to their age as Group-I (18-45 ages) and Group II (46-70 ages).

Imaging

Examinations were performed using CTI equipment (Discovery CT750 HD CT scanner). Paranasal CTI examinations were performed at 120-400 mA and 100kV, and CT slices 0.6 – 1.5 mm in thickness were obtained. Approximately 120-300 images per CTI were evaluated. In all cases, the imaging was performed using bone filter technique. It covered the entire paranasal sinuses within the sinonasal region, both axially, sagittally, and coronally. CT images were analyzed using Sectra IDS7 software, version 21.2.15.6346©2019. All evaluation was carried out; images were evaluated by three specialists (two anatomists (FY, IC) and one radiologist (OS) using PACS (picture archiving and communicating system).

Cases with disagreement were evaluated together with all observers and data entry was made by reaching a consensus.

Paranasal Sinuses

Frontal Sinus (FS): The frontal sinus is situated between the two laminae of the frontal bone, behind the superciliary arch. The two hourglass-shaped frontal sinuses are separated by a bone septum, rarely located in the anatomic midline [11] (Figure 1).

Agger nasi cell (ANC): The agger nasi cell is located in the anterior part of the superior portion of the middle turbinate. It is placed laterally below the frontal sinus, anterior to the middle turbinate on the coronal images [12]. Coronal and sagittal CTIs are most helpful in identifying the agger nasi [13] (Figure 2).

Supraorbital ethmoid cell (SOEC): Owen and Khun, in 1997 [14] (Figure 3) defined supraorbital ethmoid cells as pneumatization of the orbital plate of the frontal bone lateral to the most medial plane of the lamina papyracea.

Haller's cell (HC): The Haller's (or infraorbital) cells are an extension of ethmoid pneumatization to the orbital wall, located just beneath or inferolateral to the ethmoid bulla [15] (Figure 4).

Pneumatized Middle Turbinate: The middle turbinate attaches superiorly to the anterior skull base and posteriorly to the lamina papyracea. The posterior attachment called the basal or ground lamella and has an oblique course. This lamella is an important surgical landmark and marks the boundary between the anterior and posterior ethmoidal air cells [16]. Pneumatization of the inferior bulbous portion of the turbinate is called a concha bullosa (CB). If the pneumatization is above the level of the osteomeatal unit complex, it is called a lamellar cell (LC) or a conchal neck air cell [17] (Figures 1, 2, 3).

Statistical Analysis

Statistical analysis was performed using a dedicated software tool (SPSS 25.0 for Windows, IBM, USA). Variables were expressed as mean values, standard deviation, and range. A p-value of 0.05 was considered statistically significant, and two-sided tests were used. It was analyzed with the Brunner-Langer F2-LD-F1 model to determine whether the binary variables (existing or not) differed according to gender and age groups. Sub-analyses were performed for interacting parameters. The triple interaction between the variables, sides, genders, and age groups was evaluated using the Brunner-Langer F1-LD-F1 model using the non-parametric method, and F-statistic to obtain p-value and calculated <0.1 significant [18]. The Pearson chi-square test was used in the required sub-analysis, while the Mann-Whitney U test was utilized for other measurements. Between the binary variables, the agreement on the right and left sides was determined using the coefficients of understanding of "percent agreement, Cohen's, Conger's, and Gwet AC2 [18]. All coefficients are presented with 95% confidence intervals. Mainly due to the problems encountered with the Kappa coefficient, the Gwet AC1 coefficient, with more consistent and reliable results, was preferred. Still, Kappa and percent coefficients were also given to present more than one coefficient of agreement according to the published guide [19]. The interpretation was carried out by Gwet's probabilistic method according to the Landis and Koch scale [20]. Whether the classifications are symmetrical or not was tested with the coefficients of fit above and the exact McNemar Bowker test.

RESULTS

A total of two hundred patients met the inclusion criteria, aged between 18 and 75 (half of these were male and half were female) (Tables 1 and 2). The mean age of the patients was 46, and 49% of the patients were in Group I, and 51% were in Group II. Bilateral frontal sinuses were found 91.5% of the population, while 3.5% had frontal sinus agenesis on both sides. While 38.5% of 200 patients had bilateral SOEC, this variation was observed in 53% of the cases on at least one side (Figure 3). LCs were observed on both sides in 21.5% of the cases; they were present on at least one side in 33.5%. While ANCs were observed bilaterally in 68.5% of cases, the rate of patients with ANCs on at least one side was 84.5% (Figure 2). While the rate of bilateral HC was 24% in 200 cases, it was observed on at least one side in 43% of the cases. Bilateral concha bullosas (CBs) were observed in 19% of the cases, while CB variation on at least one side was 42%. When paranasal sinus variation on one side was detected in a patient, it was wondered if it was on the other side or vice versa. Thereby, the compatibility between the right and left sides of the patients was checked. While studying compatibility, previous studies were evaluated to obtain the optimal result by using many coefficients. Table 1 summarizes the comparison of paranasal sinus variations according to gender, age groups, and right and left sides.

Frontal sinuses were found in 189 (94.5%) on the right side and 187 (93.5%) on the left side, for a total of 376 (94%) (Table 2). The total number of absent FS was 13 (6.5%) on the right side, 11 (5.5%) on the left side, and, 24 (6.0%) in total. A slight difference between the two sides was not statistically significant ($p = 0.524$). There was also no statistically significant difference between genders ($p = 0.989$). According to age groups, sinus frontalis was present in 185 (94.4%) of the patients in Group I, and 191 (93.6%) patients in Group II. There was no statistically significant difference between Group I and Group II in terms of frequency ($p = 0.803$). Regardless of age and gender differences, the presence of FS was highly symmetrical (Table 2).

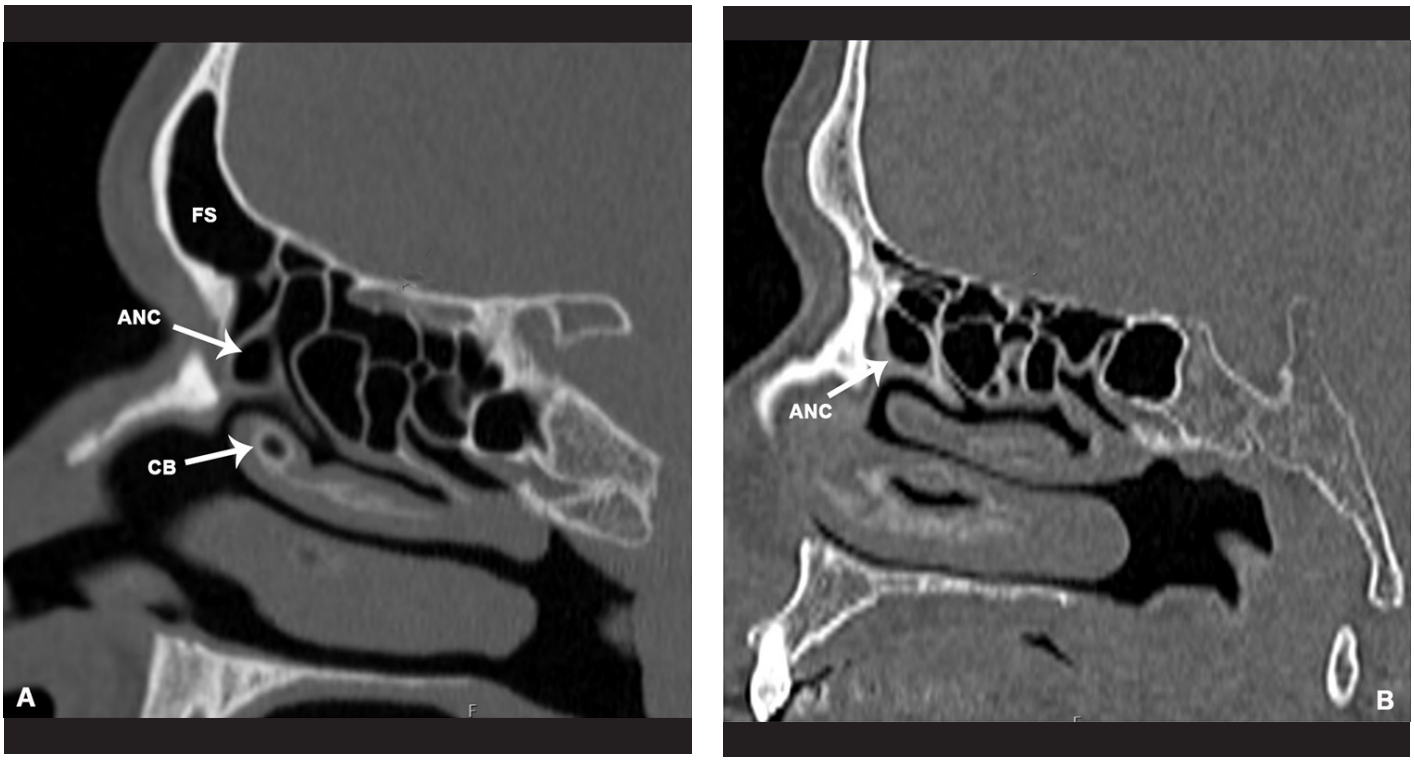

Figure 1. Sagittal cross section view of two different patients' paranasal sinus CTI.
A: Agger nasi cell (ANC), small-sized concha bullosa (CB), and frontal sinus (FS) can be seen.
B: Agger nasi cell (ANC) and frontal sinus agenesis (red asterisk). The attachment of uncinate process to the ANC is remarkable.

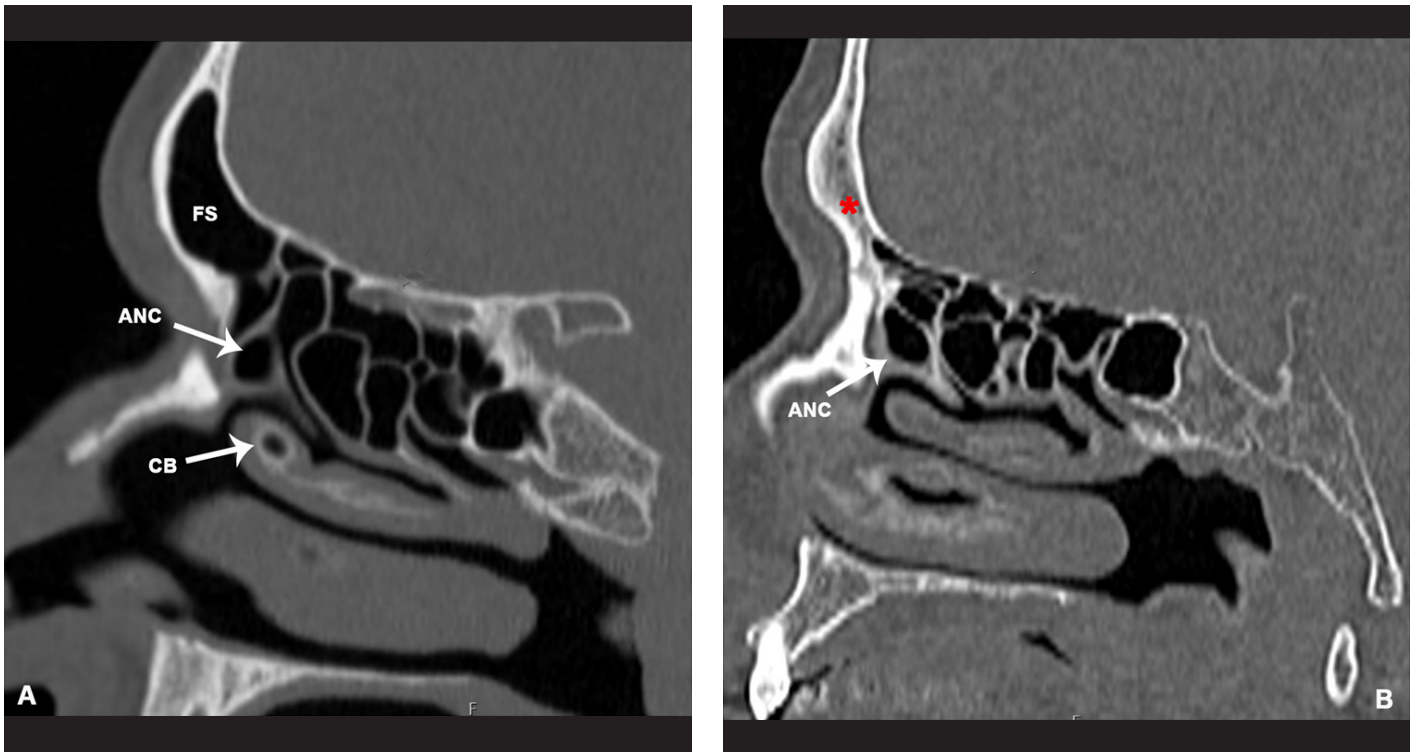

Figure 2. Sagittal (A) and coronal (B) section view of a paranasal sinus CTI. A large-sized concha bullosa (CB) and agger nasi cell (ANC) can be noticed.

SOECs were defined in 183 cases (45.8%). Eighty-five of these were on the right side (42.5%), and 98 were on the left side (49%). Approximately 42% of the total were females, and 49.5% were males. SOECs were found with a higher frequency on the left side ($p = 0.017$). Group I (43.9%) and Group II (47.5%) had no state differences. There was no statistical difference in terms of gender. Although the presence of SOECs has a high coefficient of agreement between the right and left sides of the same individual, the fact of significant symmetry cannot be claimed ($p < 0.05$) (Table 2).

A total of 306 ANC (76.5%) were identified, with an equal distribution of 50% on the right side and 50% on the left side. Among these 306 ANCs, 78.5% were female, and 74.5% of these were associated with ANC. The study observed a high level of symmetry agreement (89%) between the right and left sides in males. Group I consisted of 155 cases (79.1%), while Group II had 151 cases (74%). There were no significant differences in the presence of ANC based on age groups, sides, and genders ($p > 0.05$) as shown in Table 2. The presence of ANC was accompanied by strong symmetry (89%) between the right and left sides.

Haller's cells were found in 134 of 400 samples (33.5%). Sixty-eight (34%) of these cells were on the right, and 66 (33%) were on the left side. There were 71 HCs (35.5%) in the female group and 63 HCs (31.5%) in the male group. In age groups, there were 70 (35.7%) HCs in Group I and 64 (31.4%) HCs in Group II. There was no statistically significant difference when the presence of HCs was evaluated independently by side, gender, and age groups ($p > 0.05$). However, when the interaction of the groups with each other was examined, it was fewer (9.4%) on the left side in Group II, which was statistically significant ($p = 0.089$). The incidence of HC on the right side in Group II is 11.1%, which was higher in the female group. On the left side, there was no significant difference. This interaction between the variables was statistically significant ($p = 0.046$). Symmetry on the sides without HCs were found in 114 samples (86%). Contrastingly, HCs were present in 48 (71%) bilaterally, and the agreement between the two sides was high ($p = 0.871$) (Table 2).

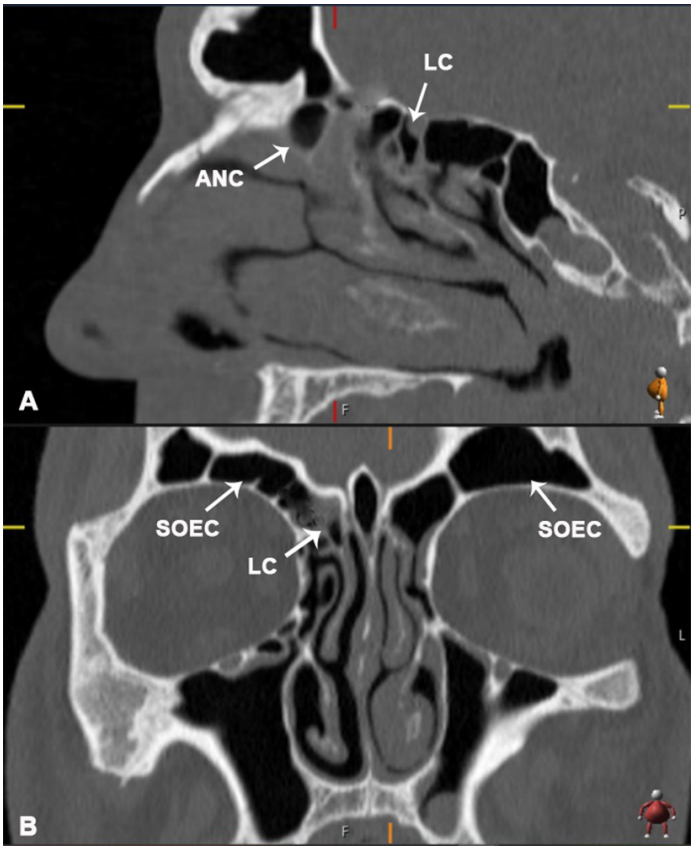

Figure 3. Sagittal (A) and coronal (B) section view of a paranasal sinus CTI. **A:** Lacrimal cell (LC) is apparent in superior attachment of middle nasal concha. **B:** Bilateral large size supraorbital ethmoid cells (SOEC) and lacrimal cell (LC) can be seen.

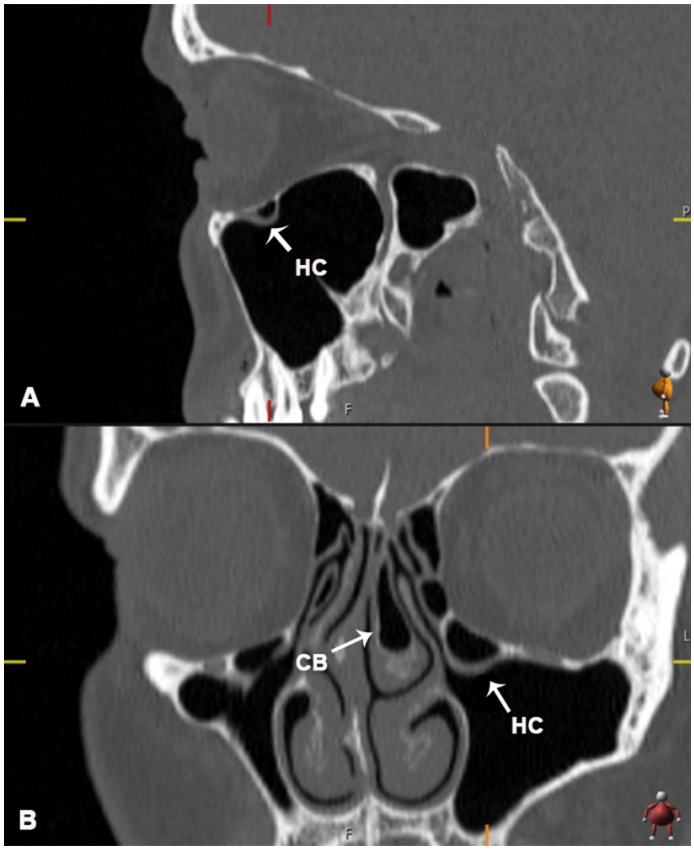

Figure 4. Sagittal (A) and coronal (B) section view of a paranasal sinus CTI. **A:** A white arrow indicates a Haller cell (HC) located at the inferior wall of the bony orbit on the left side. **B:** A well-developed concha bullosa (CB) can be seen medial to Haller cell.

Table 1. Comparison of data on paranasal sinus variations according to gender, age groups, right and left sides.

Paranasal sinuses	Gender		Age groups		Sides		Total
n (%)	Female	Male	18-45	46-70	Right	Left	
FS	188 (94.0)	188 (94.0)	185 (94.4)	191 (93.6)	189 (94.5)	187 (93.5)	376 (94.0)
SOEC	84 (42.0)	99 (49.5)	86 (43.9)	97 (47.5)	85 (42.5)*	98 (49.0)*	183 (45.8)
ANC	157 (78.5)	149 (74.5)	155 (79.1)	151 (74.0)	153 (76.5)	153 (76.5)	306 (76.5)
LCs	54 (27.0)	56 (28.0)	52 (26.5)	58 (28.5)	55 (27.5)	55 (27.5)	110 (27.5)
HCs	71 (35.5)	63 (31.5)	70 (35.7)	64 (31.4)	68 (34.0)	66 (33.0)	134 (33.5)
CB	67 (33.5)	55 (27.5)	61 (30.5)	61 (30.5)	62 (31.0)	60 (30.0)	122 (30.5)

*p<0,05. *FS: Frontal sinus, SOECs: Supraorbital ethmoidal cells, AN: Agger nasi cells, LCs: Lamellar cells, HCs: Haller's cells, CB: Concha bullosa.*

Table 2. Data on the bilaterality of the paranasal sinuses.

Paranasal sinuses, Right		Left		Compliance		Symmetry
		0	**1**	**Coefficients***	**Compliance Degree**	**P-value****
FS	0	7	*6*	0.950	0.8-1.0	0.754
	1	*4*	183	0.556	0.2-0.4	
				0.943	0.8-1.0	
SOEC	0	94	*21*	0.855	0.8-1.0	0.024***
	1	*8*	77	0.709	0.6-0.8	
				0.712	0.6-0.8	
LC	0	133	*12*	0.880	0.8-1.0	1,000
	1	*12*	43	0.699	0.6-0.8	
				0.800	0.6-0.8	
ANC	0	31	*16*	0.840	0.6-0.8	1.000
	1	*16*	137	0.555	0.4-0.6	
				0.750	0.6-0.8	
HC	0	114	*18*	0.810	0.6-0.8	0.871
	1	*20*	48	0.574	0.4-0.6	
				0.657	0.4-0.6	
CB	0	116	*22*	0.770	0.6-0.8	0.883
	1	*24*	38	0.458	0.2-0.4	
				0.601	0.4-0.6	

* From top to bottom are Percent Agreement, Cohen/Conger's Kappa, Gwet's AC, respectively.

Among 400 samples, 122 CB (30.5%) were identified. Of these, 55 (27.5%) were males, and 67 (33.5%) were females. 60 (30%) were on the left side, and 62 (31%) were on the right side. The numbers in the CB were equal between age groups. There was no statistically significant difference between gender, side, and age groups. 63% of CBs were bilateral, and the symmetry shown on the right and left sides was found to be statistically in moderate agreement (Table 2).

Lamellar cells were present in 110 samples (27.5%), found in equal numbers on the right and left sides. LCs were identified in 27% of female and 28% of male, and detected in 52 (26.5%) of 196 samples in Group I and 58 (28.5%) of 204 samples in Group II. There was no significant difference between gender, side, and age groups ($p > 0.005$). Symmetrical concordance of LCs, of which 78% were bilateral, was found to be statistically high (Table 2).

DISCUSSION

The sinonasal region is one of the more complex areas of the body, in which most anatomical variations are frequently seen. Most ANCs are anterior to the uncinate process. Still, the posterior half of the ANC has an intimate relationship with the upward extension of the uncinate process (Figure 1). They are frequently seen bilaterally and come into prominence clinically by narrowing the frontal recess opening and disrupting its drainage [21]. There is a relationship between chronic frontal rhinosinusitis, frontoethmoidal pain, and ANCs. Patients with agger nasi extension into the nasofrontal canal were reported to be twice as likely to require surgical treatment [7, 22] (Figure 1b). When patients undergoing revision functional endoscopic sinus surgery were evaluated with sinus CTI, a strong association was identified between variations due to ANCs and frontal sinus diseases [23]. The prevalence of the ANC variations has been reported to be between 7 and 98% [24]. The fact that quite different results could be obtained in studies conducted in similar ethnic communities also suggests the variability of the region. Tiwari and Goyal [25] evaluated chronic rhinosinusitis cases both with CTI and nasal endoscopy and found the prevalence to be 7%. In the study of Lien et al. [26] the prevalence was found to be 89 percent in the group of patients with paranasal sinus related disorders such as rhinosinusitis, anosmia, headache, nasal tumor, cerebrospinal fluid leak, and maxillofacial fractures. In a study conducted in Turkey [27] it was found that the most common paranasal region variation after septal deviation was ANC, and its prevalence was revealed to be 63.8%. In another CTI study conducted in Turkey [28], patients with septal deviation were examined, and the ANC was also found to have the most common variations (82%). In our study, the ANC was also found to be the most common variation, with 76% of the patient group without any disease affecting the paranasal sinus region (Table 1).

In 1942, Van Alyea described the SOEC as an ethmoid cell invading (most anteriorly) the supraorbital plate of the frontal bone [29] (Figure 3a). The frontal bone's orbital plate's air cells are known as SOECs, and a bony septum is the only thing that separates them from the frontal sinus. They are situated lateral to the lamina papyracea's most medial portion [30] (Figure 3b). The prevalence of SOECs has been reported in previous studies to range from 5.4 to 42.4% [13]. In the study of Zhang et al. [31], spiral CTIs of 202 patients were examined in sections passing through three planes; 22 SOECs were identified (5.4%), and it was stated that all SOECs arose from anterior ethmoidal cells. They also found significant correlation between frontal sinus septation and SOECs. Interestingly, Comer reported that the presence of SOEC is also associated with orbital proptosis in patients with chronic rhinosinusitis [32]. It is also seen that ethnic differences may be effective in the relationship between the presence of SOEC and frontal sinus septation [32, 33].

The unilateral or bilateral presence (symmetry) of SOEC is of clinical importance but there are few studies focusing on this point. Comer et al. [32] found the prevalence of the bilateral SOEC 12%. In their study, it was emphasized that the incidence of bilateral SOEC is higher in patients with proptosis and chronic rhinosinusitis. Elvan et al. [34], it was suggested that the presence of unilateral SOEC may be associated with migraine. In the current study, SOEC was found bilaterally in 72.6% of the patients. However, when we analyzed the cases statistically, it was understood that the probability of the presence of SOEC bilaterally in the same case was not significantly high (Table 2). The clinical importance of bilateral SOEC was emphasized in Comer's study and it was shown that proptosis and chronic rhinosinusitis were highly correlated with bilaterality. On the contrary, in Elvan's study, the presence of unilateral SOEC was shown to be associated with migraine [32].

A Swiss anatomist named Albert von Haller first described HCs in 1765 [35]. HCs, also called infraorbital cells, are air cells along the roof of the maxillary sinus, under the ethmoid bulla, and in the lowest part of the lamina papyracea, including the air cells in the ethmoid infundibulum (Figure 4). HCs have been implicated as a potential etiologic factor in recurrent maxillary sinusitis due to their negative influence on sinus ventilation. There are many studies in the literature emphasizing the relationship between HCs and various pathologies such as chronic rhinosinusitis, mucocele, and persistant headaches [7]. Studies using CTIs to identify HCs have higher detail in detecting variations than studies using panoramic radiographs because they provide a 3D examination of the region, and the prevalence appears to be higher in these cases. In 2018, Nedunchezhian et al. [36] found the prevalence of the HCs at 28.6% from panoramic radiographs of 600 patients from the Indian population. In a study conducted on 300 people with the same methodology, the prevalence of the HCs was found to be 10% in India; in another research conducted in 2021, it was figured out to be 22.1% [37]. On the contrary, HCs prevalence was found between 2.5% and 60% in the studies evaluated from CTIs of the patients [39]. HCs were found at 33.5% (134 out of 400) in the current study (Table 1).

Of these, 68 (34%) were on the right and 66 (33%) were on the left. We found that 43% of 200 patients had HCs; 24% of these were bilateral and 19% unilateral (Table 2). Chaudhari et al. [37] found the HCs' prevalence to be 10% (30 out of a total of 300 Indian adults); 14 of these (4.7%) were unilateral, and 16 of these (5.3%) were bilateral. In Wanamaker's [40] study, HCs were found bilaterally in 11% of the cases and unilaterally in 9%. In another study conducted by Ahmad et al., bilaterality of the HCs was found to be 18.5% and unilaterality was 19.7% [41]. In our study, HCs were found mostly bilateral, and the prevalence of cases with unilateral HCs was higher compared to the literature (Tables 1-2). This difference may be a specific situation of the population used in the study, or it may be due to differences in detail in radiological imaging or differences in the anatomical definition of HC [36].

The middle turbinate is an essential part of the ethmoidal labyrinth. Although it is reported to be a necessary landmark for endoscopic sinus surgery, it is controversial due to variations in size, shape, and symmetry [17]. Concha bullosa variations are often regarded as a variation rather than a pathological condition. Although the posterior ethmoidal cells are a rare origin of the pneumatization, CB's air is mainly derived from the anterior ethmoid cells. Basically, three CB groups are widely known, which are named by Bolger et al. as lamellar, bulbous, and extensive [42]. The lamellar type is the pneumatization of the vertical lamella, the bulbous type is the pneumatization of the bulbous part, and extensive CB is the pneumatization of both lamellar and bulbous segments [42]. In our study, we examined the lamellar type as LC and the other two types as CB. Since they are mostly asymptomatic and detected incidentally; the frequency of those is between 13-56% [34] and most of them are found bilaterally. Although a small pneumatization is not clinically significant, a large CB might be associated with a septal deviation that obstructs the drainage pathway of the antrum by distorting the uncinate process and narrowing the infundibulum, resulting in chronic sinusitis and headache [43]. Bolger [42] stated that the most common type was the lamellar type (46.6%), and the second most common was the extensive type (44%). In another study, the prevalence of lamellar cells was found to be 47%; one-third of them were unilateral (14.9%) and two-thirds (32.8%) were bilateral [44]. In our study, the prevalence of the LC was 27.5% and the CB was 30.5%. The prevalence of cases with bilateral CB was found to be 62.3%, which is less common than bilateral LC occurrence (78.2%) and this result is compatible with the results of the study conducted by Calvo-Henriquez. Bulbous and extensive types were identified as CB in the current study, in which 23% were unilateral and 19% bilateral, so the results of our study differ from those mentioned before [34].

The pneumatization process of frontal sinus cells (FSs) takes place primarily within the first four months of life. These cells become visible on radiological images around the seventh year of life, and their development reaches maturity at approximately 20 years of age [45]. The FSs develop from the posterior part of the frontal or suprabullar recess, and, each sinus develops separately; therefore, a remarkable asymmetry may occur between the left and right sinuses in the same person [15]. Variations in the frontal sinus cells are of clinical importance due to their close relationship with the frontal recess and ostium, which may restrict the frontal sinus outflow [46, 47]. They can be found unilaterally, bilaterally absent or completely agenesic [46]. Although the absence of frontal sinus has been reported in various syndromes (i.e. Micrcornea-glaucoma-absent frontal sinuses syndrome), it has been reported that the frequency of these cases may vary with ethnicity and gender [46]. In addition, some researchers suggest that mechanical stress caused by chewing, local inflammations, and geographical conditions may affect frontal sinus development [48]. The prevalence of absent frontal sinus in the Turkish population was found 0.78-6.4 [11]. In the current study, bilateral absence of the FS was found to be 8.5%, and unilateral absence was 2.5%. In the study of Çakır et al. [11] in which they examined 410 patients in Turkey, the prevalence of bilateral frontal sinus agenesis was 0.73%; unilateral frontal sinus agenesis was 1.22%. In the study of Danesh-Sani et al. [46] in Iran, 565 adults were examined, and the prevalence of bilateral FS agenesis was 8.32% and the prevalence of unilateral agenesis was 5.66%. In a study conducted in China, 196 patients were evaluated, and it was observed that the FSs were absent on one side in 12.9% [33] (Figures 1, 3, 4).

Retrospective design of the study was the major limitation. Patients defined as healthy adults that apply to the clinic with a specific complaint and an undiagnosed pathology may have been affected by the anatomy of the sinonasal region. However, this limitation was minimized by excluding people with a medical history and new diagnoses of diseases that may affect the anatomy of the paranasal sinus. At last, other rare variations due to the study design were not discussed. The results of our study should be supported by prospective studies in healthy population. Examining the relationships of cases with variation

with clinical findings that change with age and gender will be important in guiding clinical interventions.

In conclusion, paranasal sinus variations and bilateral-unilateral presence patterns in healthy adult Turkish population were investigated in our study. The most common paranasal sinus variation was ANC. SOEC was the second most common and followed by the HC and LC. The rarest variation was frontal sinus agenesis. The variation with the highest prevalence of bilateral is SOEC. In addition, the bilateral incidence of LC is higher than the others. The results of our study differ from the literature, as the prevalence of HC is found to be close to the prevalence of bilateral occurrence. Considering the results of our study during preoperative image evaluation in paranasal region surgery is important in terms of reducing complications and increasing the success of the procedure.

Informed Consent: The patients signed the written informed consent.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Original Research

Gender Estimation with Parameters Obtained From the Upper Dental Arcade by Using Machine Learning Algorithms and Artificial Neural Networks

Halil Şaban Erkartal[1], Melike Tatli[1], Yusuf Secgin[2], Seyma Toy[2], Suayip Burak Duman[3]

[1] Department of Anatomy, Faculty of Medicine, Graduate School of Education, Karabük University, Karabük, Turkey
[2] Department of Anatomy, Faculty of Medicine, Karabük University, Karabük, Turkey
[3] Department of Oral and Maxillofacial Radiology, Faculty of Dentistry, İnönü University, Malatya, Turkey

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Correspondence
Yusuf Secgin, PhD Student
Address: Department of Anatomy, Faculty of Medicine, Karabük University, Karabük, Turkey
E-mail: yusufsecgin@karabuk.edu.tr

ABSTRACT

Objective: The aim of this study is to predict gender with parameters obtained from the upper dental arch by using machine learning algorithms (ML) machine learning algorithms and artificial neural networks to provide optimum aesthetics, functionality, long-term stability, diagnosis and treatment intervention in orthodontics, forensic medicine and anthropology.

Methods: The study was conducted on cone-beam computed tomography (CBCT) images of 176 individuals between the ages of 18 and 55 who did not have any pathologies or surgical interventions in their upper dental arcade. The images obtained were transferred to RadiAnt DICOM Viewer program in Digital Imaging and Communications in Medicine format and all images were brought to orthogonal plane by applying 3D Curved Multiplanar Reconstruction. Length and curvature length measurements were performed on these images brought to orthogonal plane. The data obtained were used in ML algorithms and artificial neural networks input and rates of gender estimation were shown.

Results: In the study, an accuracy ratio of 0.86 was found with ML models linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), logistic regression (LR) algorithm and an accuracy ratio of 0.86 was found with random forest (RF) algorithm. It was found with SHAP analyser of RF algorithm that the parameter of width at the level of 3rd molar teeth contributed the most to gender. An accuracy rate of 0.92 was found as a result of training for 500 times with multi-layer classifier perceptron (MLCP), which is an artificial neural network (ANN) model.

Conclusion: As a result of our study, it was found that the parameters obtained from the upper dental arcade showed a high accuracy in estimation of gender. In this context, we believe that the present study will make important contributions to forensic sciences.

Keywords: Upper dental arcade, cone-beam computed tomography, estimation of gender, machine learning algorithms, artificial neural networks

INTRODUCTION

Identification of individuals is one of the most important and challenging situations that can be encountered when an accident or disaster occurs. In such cases, biological profile should be created for forensic identification and morphological identification. Biological profile includes gender, ancestry, bone-tooth age, height and physical structure. Gender estimation approaches are also used in anthropological studies in addition

to forensic studies. Estimation of gender by using human bones is one of the important tasks that anthropologists must fulfil in identification process for forensic scientists and law enforcement officers [1]. For this reason, adding new ones to the bones which are known to show sexual dimorphism becomes an important issue.

The importance of the maxilla in the facial skeleton results from its central position providing structural support to the face and the importance of the upper jaw in facial structure [2, 3]. The hard palate is formed by the fusion of the two palatine processes of the maxilla and the two horizontal parts of the palatine bone [3, 4]. Fusion of the palatine processes forms the anterior nasal floor and the anterior inferior border of the pyriform aperture [2, 3]. Incisive, canine, premolar, molar teeth mandibular and maxillary arch lengths are important parameters that can be used in gender determination. Especially canine and molar teeth are known to be widely used for gender determination due to their morphological variability and durability [5]. They are considered as a reliable source according to a large number of researchers [5-7]. The formation and development of dental arches is affected by a large number of factors such as unbalanced muscle strength in the face and mouth, vital habits, type of malocclusion, eruption changes of teeth, movement of teeth after eruption, other bones in the face, gender and ethnicity. In particular, there is a research topic for the explanation of dental arch forms and different features of the upper anterior teeth [8-11].

Structures of the upper dental arcade can retain their integrity after death or even after severe damage. Although it can be seen that gender dimorphism of the hard palate has been the subject of research for many years, it can also be seen that a complete consensus has not been reached [12-15].

Main Points;

- Can gender be predicted with high accuracy and reliability using machine learning algorithms from upper dental arcade?
- Can gender be predicted with high accuracy and reliability using neural networks from the upper dental arcade?
- Is upper dental arcade an important biomarker in determining gender?

Although machine learning algorithms (ML) have been a research topic of many years in the field of engineering, it is a recent issue in the field of health. Since ML algorithms are computer based algorithms, they can show the association between input and output with a higher accuracy than individual observations. Artificial neural networks (ANN) are also computer based models and they stand out as a result of their high estimation rate and good non-linear data processing [16-20]. In recent years, ANN and ML are technological developments that we frequently encounter and make great contributions to forensic medicine [21].

The aim of this study is to show the role of length and width parameters of canine, molar, upper dental arcade taken with cone-beam computed tomography (CBCT) by using machine learning algorithms and artificial neural networks on gender estimation in Turkish population.

MATERIALS AND METHODS

Study population and CBCT scanning protocol

The study was conducted with the 2023/4337 issued decision of non-interventional local ethics committee. CBCT images of 86 female and 90 male between the ages of 18 and 55 were included in the study. Exclusion criteria were determined as not being within the predetermined age range and not having surgical intervention and pathology in the upper dental arcade.

CBCT images were obtained by using NewTom 5G (Verona, Italy) device. Screening protocol was determined as110 kVp, 1-11 mA, 3.6 s.

Image processing

The images that met the inclusion criteria between 2020 and 2023 taken from the Picture Archiving Communication Systems (PACS) of the hospital were reviewed retrospectively. The scanned images were transferred to personal work station Windows based RadiAnt DICOM Viewer program in Digital Imaging and Communications in Medicine (DICOM) format. The transferred images were obtained by using the 3D Curved Multiplanar Reconstruction (MPR) console of the program and three images were obtained in axial, coronal and sagittal planes. All images were brought to the orthogonal plane by determining the line passing through the palatine process of maxilla in the images. Length and curvature length measurements were performed by overlapping the axial image in the orthogonal plane (Figure 1).

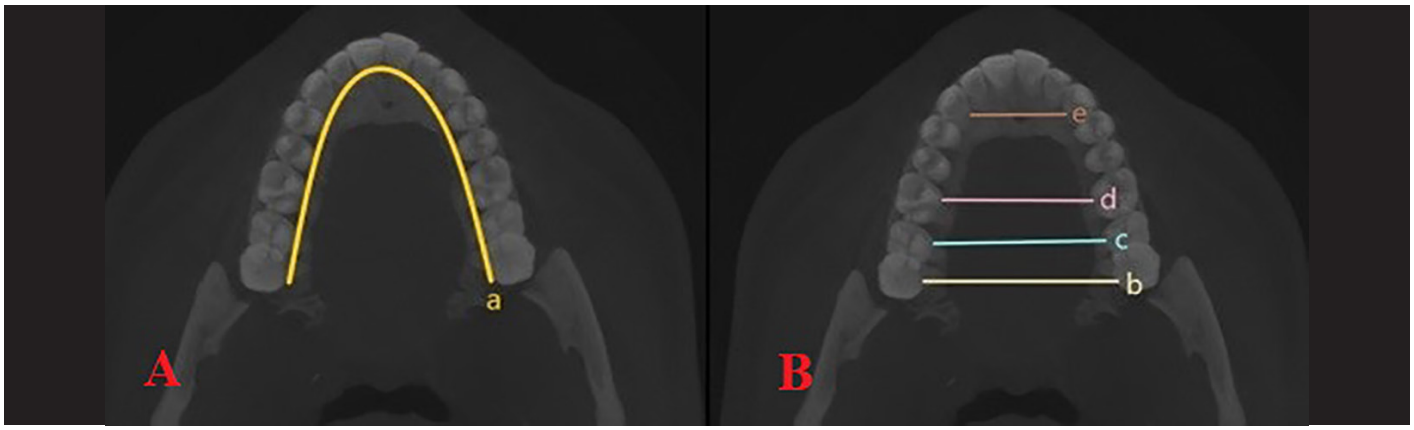

Figure 1. Demonstration of parameters (Figure 1-A, a: Curvature length of the upper dental arcade, Figure 1-B, b: Width at the level of third molars, c: Width at the level of second molars, d: Width at the level of first molars, e: Intercanine width)

Parameters were;

- Curvature length of the upper dental arcade (UDA-CL): Curvature length of all teeth starting from right and left maxillary third molars
- Intercanine width (IC-W): Width between inner edges of left and right maxillary canines
- Width at the level of first molars (M1-W): Width between inner edges of right and left first molars
- Width at the level of second molars (M2-W): Width between inner edges of right and left second molars
- Width at the level of third molars (M3-W): Width between inner edges of right and left third molars

Implementing ML Algorithms and ANN

Python 3.9 programming language and scikit-learn1.1.1 framework were used in ML and ANN modelling. The modelling was performed by using Monster Abra A7 V12.5 model personal computer with i5 processing system and 8 Gb Ram. In ML and ANN modelling, test set was determined as 20%, while the training set was determined as 80%. Linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), logistic regression (LR), random forest (RF) algorithms were used in ML modelling. No extracting or cleaning was applied on the data for the ANN model to reflect the reality. Multi-layer classifier perceptron (MLCP) was preferred as ANN model. Six neurons were used in the input layer, while 2 neurons and 2 hidden layers (first with 18 neurons and second with 12 neurons) were used in the output layer. The network in this topology was retrained for 100, 500 and 1000 times for a real learning to occur. Accuracy (Acc), Specificity (Spe), Sensitivity (Sen), F1 score (F1) values were used as performance criteria in both models (ML-ANN). In our study, the effect of each parameter on the overall result was evaluated using the SHAP analyzer of the RF algorithm.

Equation 1. (TP; True positive, TN; True negative, FP; False positive, FN; False negative).

Statistical Analysis

In descriptive statistics of the parameters, mean and standard deviation were included for those with normal distribution, while median, minimum and maximum values were included for those that were not normally distributed. Normality distribution was tested with Anderson Darling test. Minitab 17 package program was used for descriptive statistics.

RESULTS

In the study conducted on 86 female and 90 male between the ages of 18 and 55, it was found that the parameters of age and UDA-CL were not normally distributed, while the other parameters were normally distributed. Descriptive statistics of the parameters which were not normally distributed are shown in Table 1.

Descriptive statistics of the normally distributed parameters are shown in Table 2.

As a result of ML algorithms, the highest Acc rate was founds as 0.86 with LR, LDA, QDA algorithms (Table 3).

Confusion matrix obtained as a result of ML algorithms is shown in Figure 2.

Table 2. Descriptive statistics of the normally distributed parameters

Parameters (cm)	Gender	Mean	Standard Deviation
IC-W	Male	2.560	0.217
	Female	2.402	0.218
M1-W	Male	3.655	0.312
	Female	3.532	0.356
M2-W	Male	4.002	0.377
	Female	4.050	0.384
M3-W	Male	4.257	0.386
	Female	4.793	0.430

Table 3. Performance criteria obtained as a result of machine learning algorithms

Algorithms	Acc	Spe	Sen	F1
RF	0.81	0.81	0.81	0.81
LR	0.86	0.86	0.86	0.86
LDA	0.86	0.87	0.86	0.86
QDA	0.86	0.87	0.86	0.86

The effect of parameters on the overall result was examined with SHAP analyser of RF algorithm and it was found that M3-W parameter had the highest contribution (Figure 3).

Table 4 includes the mean performance criteria obtained as a result of training for 100, 500 and 1000 times in MLCP model. The highest mean performance was obtained as a result of training for 500 times.

Figure 4 shows the confusion matrix table obtained as a result of training for 500 times.

Higher accuracy results were obtained with the MLCP model than the ML model.

Table 4. MLCP mean performance criteria

Number of Education	Acc	Spe	Sen	F1
100	0.86	0.86	0.86	0.86
500	0.92	0.92	0.92	0.92
1000	0.83	0.83	0.83	0.83

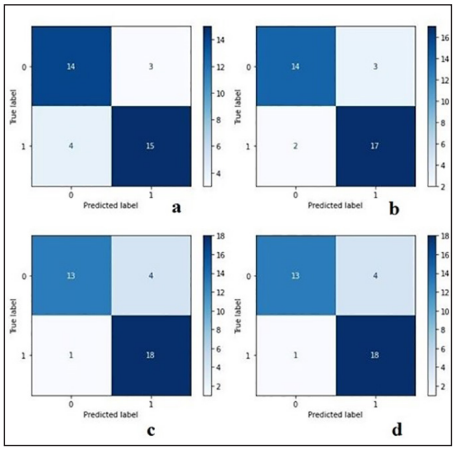

Figure 2. Confusion Matrix table of the ML modelling (a: Random Forest, b: Logistic Regression, c: Linear Discriminant Analysis, d: Quadratic Discriminant Analysis)

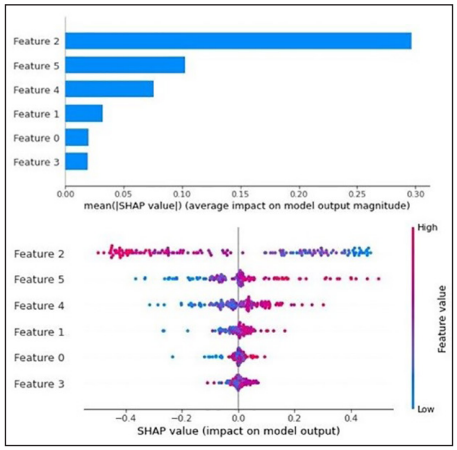

Figure 3. SHAP analyser *Feature 2: Width at the level of third molars, 5: Intercanine width, 4: Width at the level of first molars, 1: Curvature length of the upper dental arcade, 0: Age, 3: Width at the level of second molars

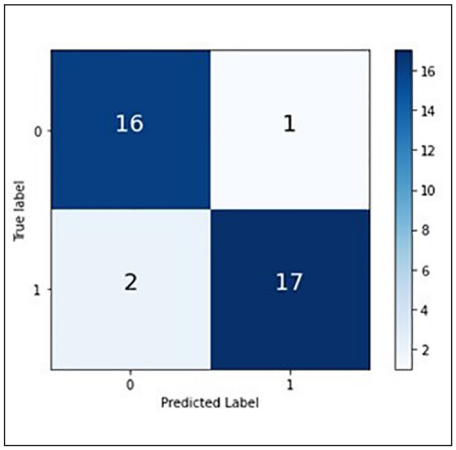

Figure 4. Confusion matrix table of MLCP training for 500 times

DISCUSSION

When the data obtained in the study were transferred to ML and ANN, the highest accuracy rate for a possible gender estimation was found by MLCP, which is used as ANN model. In the measurements, accuracy rate was found as 0.92 when MLCP was trained 500 times. When these results were examined and the related parameters were added, it was found that MLCP trained 500 times could estimate the gender of 92 individuals out of 100 correctly. All of the parameters were examined one by one with SHAP analyser of RF algorithm and their effects on the general result were analyzed and it was found that M3-W was the parameter that increased accuracy rate most. The effects of the other parameters on accuracy rate can be listed as follows: the parameter with the highest effect after M3-W was IC-W, followed by M1-W, UDA-CL, age and finally M2-W with the lowest effect. An accuracy rate of 0.86 was found as a result of LR, LDA, QDA algorithms obtained with ML.

In a study conducted by Bishara et al. [22], individuals were divided into certain age groups, their maxillary arch lengths were measured and maxillary arch length was found as 73.2 mm in males and as 71.1 mm in females for 26 years of age, while it was found as 72.2 mm in males and as 70.1 mm in females for 45 years of age. In another maxillary arch length measurement study conducted by Alam et al. [23] with their own reference points, maxillary arch length was found as 77.4 mm in males and as 74.5 mm in females. In a study conducted by Hashim et al. [24], mean maxillary arch length was found as 74.01 mm in males and as 72.36 mm in females. According to the measurement found in the study, mean UDA-CL median value was found as 11.090 cm in males and as 11.130 cm in females. In our study, unlike general data, it was found that females had higher maxillary arch length than males. The parameters used, changes in populations and differences in methods may have caused the different results.

In a study they got the measurements from buccal cusps, Burris et al. [25] found mean IC-W as 33.8 mm in males and as 32.6 mm in females. In a similar anthropometric measurement study Alvaran et al. [26] conducted on individuals aged between 5 and 17, mean IC-W was found as 33.3 mm in males and as 32.4 mm in females. In a study conducted by Rao and Kiran [27], mean IC-W was found as 35.08 mm in males and as 33.42 mm in females. Al-Omari et al. [28] found mean IC-W as 35.28 mm in males and as 33.92 mm in females. Muhammad et al. [29] found mean IC-W as 36.57 mm in males and as 35.82 mm in females. The results of the aforementioned studies and the present study are in parallel. In our study, mean IC-W was found as 2.560 in males and as 2.402 in females; mean M1-W was found as 3.655 in males and as 3.532 in females; mean M2-W was found as 4.002 in males and as 4.050 in females and mean M3-W was found as 4.257 in males and as 4.793 in females. We think that the small difference that occurs is due to the population difference.

In the literature, Burris et al. [25] found mean M1-W as 50.1 mm in males and as 48.0 mm in females and found that mean value was higher in males. In a study conducted on individuals aged between 5 and 17, Al-varan et al. [26] found that males had higher means than females. In a study based on their own measurement points, Adriana et al. [30] found mean M1-W as 49.36 mm in males and as 46.75 mm in females and found that M1-W was higher in males. In a study they conducted their own measurement points, Al-Omari et al. [28] found mean width between first molars as 48.18 mm in males and as 45.96 mm in males. In a study based on their own reference points, Mahasweta et al. [31] found mean M1-W as 32.67 mm in males, as 31.64 mm in females. According to the data found in our study, mean M1-W was 3.655 cm in males and 3.532 cm in females. Similar results were found in a large number of intermolar width measurements. It was found that males had higher maxillary M1-W than females and thus maxillary arch at the level of 1st molar was wider [32]. We think that the width in males may be caused by sex hormones.

In the study by Burris et al. [25], mean M2-W width was found as 55.7 mm in men and as 53.7 mm in females. Unlike other studies on mean M2-W, the results were higher in females than in males. In addition, unlike other studies, UDA-CL on maxillary bone was found to be longer in females than in males. We believe that these differences may be due to the ethnicity, living conditions, nutrition type of the individuals in the population measurements were made, anatomical differences of bones or different reference points and measurement methods. Sufficient information could not be found in the literature review conducted for M3-W.

CONCLUSION

Since the identity of individuals needs to be estimated quickly in events such as war, natural disasters or wars which deeply affect the society, CBCT technology and MLCP used as ANN model in this study showed that high accuracy can be obtained by minimizing this time. It is thought that the parameters taken from the maxilla in this study will contribute to studies on

gender estimation and make these studies stronger.

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Informed Consent: The study is a retrospective study and was carried out by scanning the existing images in the hospital archive system.

Conflict of interest: There is no conflict of interest.

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Ethical Approval: This study was approved by the 2023/4337 decision of the Inonu University non-invasive local ethics committee.

Author Contributions: Conception: YS; ST - Design: YS; ST - Supervision: YS; ST - Fundings: -Materials: YS; HE; MT - Data Collection and/or Processing: SD; YS; HE; MT - Analysis and/or Interpretation: YS - Literature: HE; MT - Review: ST; SD; YS; HE; MT - Writing: ST; SD; YS; HE; MT - Critical Review: ST; SD; YS; HE; MT.

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Original Research

Morphology and Topography of the Nutrient Foramina in the Shoulder Girdle and Long Bones of the Upper Extremity

Ömer Faruk Cihan[1], Süreyya Toma[1]

[1] Department of Anatomy, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey

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Correspondence
Ömer Faruk Cihan
Address: Department of Anatomy, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
E-mail: omerfarukcihan@hotmail.com

ABSTRACT

Objective: The most principal nutrition source of a bone is nutrient arteries. They are important at every stage of bone development. A nutrient artery enters a bone through the nutrient foramen, the largest hole on the outer surface of the bone. The foramen is important both morphologically and clinically.

Methods: A total of 414 adult human dry bones were investigated in this study to identify topographic and morphological features of nutrient foramina in the scapula, clavicle, humerus, radius and ulna. Nutrient foramina were examined with a hand lens. Their dimensions and directions were determined with a 21-gauge needle, and thus major foramina were detected. Positions of nutrient foramina were noted according to surfaces of the bones, and to segments separated as proximal, middle and distal by calculating foraminal index.

Results: A single nutrient foramen was found in 71% of our samples. We observed that 94.2% of foramina in the clavicle, 89.3% of foramina in the humerus, 51.3% of foramina in the radius, and 67.7% of foramina in the ulna were located in the middle 1/3 segment of the bones.

Conclusion: On account of pathologies associated with the nutrient foramen, our findings may be helpful for surgeons to design applications performed in the region. In addition, we think that our data by contributing to the literature may be a resource for clinicians due to the importance of the nutrient foramen for surgical procedures.

Keywords: Nutrient foramen, nutrient arteries, foraminal index, upper limb, long bone

INTRODUCTION

Bones are the structures that form the passive element of the movement system and form the skeleton in the human body. Bone tissue is a vascularized type of dense connective tissue [1, 2]. Bones are supplied by the nutrient, metaphyseal, epiphyseal, and periosteal artery [1]. The most prominent nutrition of the bone is provided by the nutrient artery, and this artery is an independent branch of the adjacent arteries located outside the periosteum [3]. During the prenatal and postnatal development of the bone, the nutrient artery is essential for the development of the diaphysis and epiphyseal cartilage [4]. The nutrient artery enters the bone through the nutrient foramen (FN), the largest foramen on the outer surface of the bone [5]. The entry site of the nutrient artery into the bone tissue was first described by Havers in 1691 [6]. FNs are the external opening of the nutrient canal and are distinguished from other foramen on the bone surface by the presence of a prominent vascular groove [7]. The nutrient artery enters the bone tissue through these holes called the nutrient foramen and feeds the bone along the length of the bone through channels called nutrient canal [8].

FN examined in the presented study has both morphological and clinical significance. The vascular system of bone is closely associated with some pathologies such as fracture healing or acute hematogenic osteomyelitis [4]. Healing is delayed in stress fractures due to the accompanying rupture of the nutrient artery [9]. Especially during puberty, the nutrient artery provides 70-80% of the nutrition of the bones. When bone nutrition is compromised, less vascularization of the epiphyseal plate results in medullary bone ischemia [7]. In free vascularized bone grafts, it is very important to protect the nutrient artery entering the bone from the FN. It is important to analyze the anatomy of FN in microsurgery, vascularized bone transplants, joint replacement treatments, and reconstructive surgeries. The nutrient artery should be preserved in order to maintain the presence of osteocytes and osteoblasts that have an effect on the healing process and the union of the bone graft, which is ideal for free transplantation [4, 9]. By knowing the location and variations of the FN, the placement of the internal fixation devices can be made appropriately [5]. Inappropriate treatment or poor surgical techniques may cause rupture of the FN or nutrient artery. This leads to additional interventions that need to be repeated [10, 11]. Detailed data on bone nutrition are always important in the development of new transplantation and resection techniques in orthopedics [4]. Therefore, understanding the topography of FN located on the surfaces of bones is critical to the success of surgical procedures and outcomes.

The aim of this study is to understand the topography and morphology of FN on the surfaces of bones. This region contributes to surgical procedures and increases the success of surgical results. For this purpose, to determine, examine and observe the number, location, size and direction of FN in human shoulder girdle bones and upper extremity long bones.

Main Points;

- Detailed knowledge of vascularization in upper extremity bones
- Determination of safe area in orthopedic surgery
- To preserve FN, reduce complications and increase the success rate of surgical intervention

MATERIALS AND METHODS

A total of 414 adult human dry bones (clavicle (61), scapula (59), humerus (103), ulna (89), radius (102)) from XXX University Faculty of Medicine, Department of Basic Medical Sciences and Anatomy were included in the study. Those with major abnormality of dry bones of unknown age and sex were excluded from the study.

Considering the following data, FNs in the diaphysis of each bone were studied:

Number and Location of FN

FNs were observed using a 90 mm handpiece so as not to miss the smallest FN. In order to determine the FN topography on the bones in detail, surfaces were determined in each bone. Their positions relative to the determined surfaces were noted.

Foraminal index (FI)

FI was calculated for the location of the FN in other bones except the scapula, and their segmental location was determined. FI was calculated with the Hughes formula, which is widely used in the literature [12].

$FI = (PM/LB) \times 100$

(PM: distance from the proximal point of the bone to the Major FN (MFN), LB: Length of the bone)

PM was measured with a digital caliper with an accuracy of 0.01 mm.

Determination of the total length of the bone

Total bone length was measured manually with a mechanical steel caliper [13]. How bone length measurements are made is shown in Figure 1.

Segmental calculation to foraminal index

FI was used to identify segments of long bones. The location of the FN relative to the FI has been divided into three sub-segments as indicated below [5].

- Tip I: FI≤33.33, in the proximal third of the bone.
- Tip II: FI 33.33-66.66, in the middle third of the bone.
- Tip III: FI ≥66.66, in the distal third of the bone.

FN Size and Direction

MFN was determined by calibrating the foramen with a hypodermic needle not smaller than the size 21, by including well-defined FNs in the diaphysis part of the bone [4]. Foramen where the needle could not enter were considered as secondary

FN and were not included in the calculation of FI. A rigid wire was passed through the FN opening, and its direction was determined and then confirmed with a hypodermic needle (Figure 2).

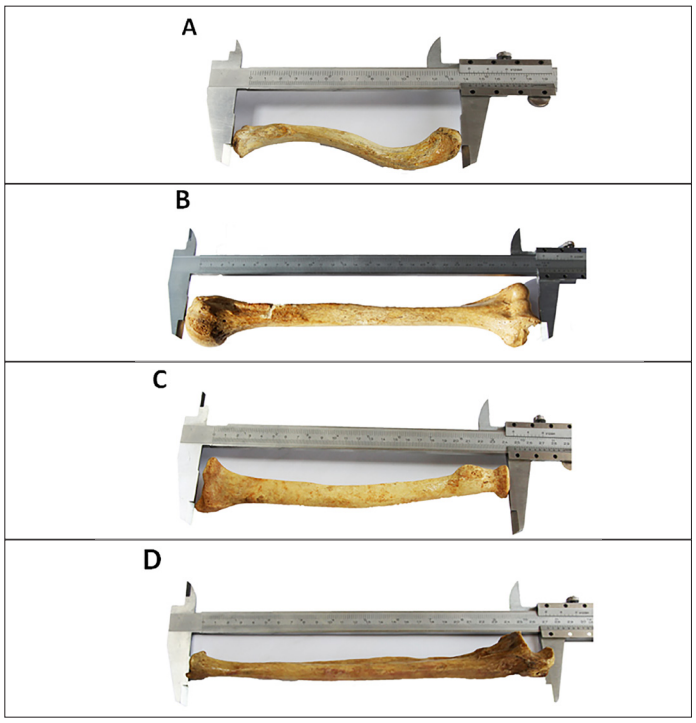

Figure 1. Measurements of the bone lengths (clavicle, humerus, radius and ulna respectively)

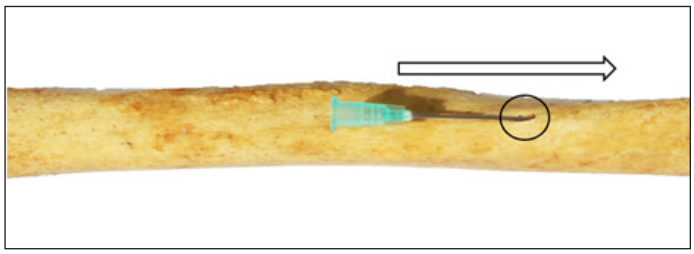

Figure 2. Detection of FN

Photographing

Photos were taken using Canon eos 700d camera and canon zoom lens ef-s 18-135mm lens. The bone photos taken were cleaned with Adobe Photoshop CS6 program.

Statistical Analysis

Whether the obtained data were suitable for normal distribution was evaluated with Shapiro wilk and Kolmogorov smirnov tests. Sample T-Test (Independent samples t test) was used to compare the variables with normal distribution in two independent groups. The Man Whitney U test, which is a non-parametric test, was used for the variables that did not fit the normal distribution. For numerical variables, mean±standard deviation values were given in descriptive statistics. SPSS statistics 20.0 package program was used for all statistical analyses. $P<0.05$ was considered significant.

RESULTS

Number of FN

The FN numbers detected in the shoulder girdle and upper extremity bones are given in Table 1 in detail. The mean number of FN in the scapula was 3.92 ± 1.38, and the mean number of FN in the clavicle was 1.68 ± 0.78. The mean number of FN in the humerus was 1.59 ± 0.91, the mean number of FN in the radius was 1.06 ± 0.22, and the mean number of FN in the ulna was 1.16 ± 0.47. When the number of FNs was compared between the parties, there was no statistically significant difference between the parties in any of the bones ($p>0.05$) (Table 1).

Total Bone Length

The mean length values of the 4 bones (clavicle, humerus, radius and ulna) examined are given in Table 2. When the bone lengths were compared between the sides, it was found that the radius of the right side was significantly larger than the left ($p=0.002$). There was no statistically significant difference in other bones ($p>0.05$) (Table 2).

PM, Distance from the proximal point of the bone to the Major FN (MFN)

PM values of the examined bones are given in Table 3. While the PM value of the right radius was significantly higher than the left ($p=0.008$), no statistically significant difference was found between the PM values of the other bones ($p>0.05$) (Table 3).

Foraminal Index

FI values of the examined bones are given in Table 4. There was no statistically significant difference between the parties in terms of FI ($p>0.05$) (Table 4).

Location of FN

Segmental position of the FN according to the FI

Position of the MFN are given in Table 5. FNs detected in the clavicle, humerus, radius and ulna were mostly found in the middle third of the bone (Table 5). The positions of the FNs by segment were verified by calculating FI. Of the 198 MFNs examined according to FI, 38 (19.1%) were Type I, 152 (76.7%) were Type II, and 8 (4%) were Type III.

Table 1 Comparison of FN number characteristics for right and left sides in shoulder girdle and upper extremity bones

Shoulder Girdle and Upper Extremity Long Bones	N		Number of FN	Mean ±SD (mm)	p
Scapula	R	30	111	3.72 ± 1.43	0.197
	L	29	116	4.12 ± 1.33	
Clavicle	R	31	43	1.48 ± 0.73	0.050
	L	30	47	1.88 ± 0.83	
Humerus	R	52	78	1.59 ± 1.01	0.507
	L	51	75	1.60 ± 0.81	
Radius	R	49	45	1.02 ± 0.14	0.093
	L	53	50	1.11 ± 0.31	
Ulna	R	38	35	1.20 ± 0.55	0.664
	L	51	52	1.13 ± 0.40	

N: Number of bones, SD: Standard deviation, R: Right, L: Left

Table 2 Findings of the comparison of bone lengths for the right and left sides of the bones

Bones	Side	N	Mean ±SD (mm)	p
Clavicle	R	31	140.33 ± 2.49	0.982
	L	30	140.42 ± 3.17	
Humerus	R	52	304. 39 ± 20.04	0.838
	L	51	303.54 ± 20.22	
Radius	R	49	241.28 ± 16.47	0.002*
	L	53	229.41 ± 18.14	
Ulna	R	38	249.64 ± 18.96	0.542
	L	51	246.80 ± 19.60	

N: Number of bones, SD: Standard deviation, R: Right, L: Left

* There is a statistically significant difference ($p<0.05$).

Table 3 Comparison of PM for right and left sides in bones

Bones	Side	N	Mean ±SD (mm)	p
Clavicle	R	31	74.17 ± 12.92	0.343
	L	30	77.67 ± 13.69	
Humerus	R	52	172.49 ± 23.17	0.243
	L	51	166.68 ± 25.26	
Radius	R	49	85.09 ± 12.84	0.008*
	L	53	78.43 ± 9.34	
Ulna	R	38	98.37 ± 19.42	0.084
	L	51	91.42 ± 12.41	

N: Number of bones, SD: Standard deviation, R: Right, L: Left, PM: Distance from the proximal point of the bone to the Major FN

* There is a statistically significant difference ($p<0.05$).

Table 4. Findings of the comparison of FI values for the right and left sides of the bones

Bones	Sides	N	Mean ±SD (mm)	p
Clavicle	R	31	52.80 ± 7.55	0.436
	L	30	54.50 ± 7.84	
Humerus	R	52	56.68 ± 5.56	0.181
	L	51	54.87 ± 7.33	
Radius	R	49	34.93 ± 4.01	0.578
	L	53	35.18 ± 4.60	
Ulna	R	38	37.36 ± 5.98	0.882
	L	51	37.17 ± 4.40	

N: Number of bones, SD: Standard deviation, R: Right, L: Left, FI: Foraminal index

Table 5. Position of MFNs relative to segments in bones (numbers and percentages)

Bone	MFN	Proximal 1/3(%)	Middle 1/3 (%)	Distal 1/3 (%)
Clavicle	52	-	49 (94.2%)	3 (5.7%)
Humerus	47	-	42 (89.3%)	5 (10.6%)
Radius	37	18 (48.6%)	19 (51.3%)	-
Ulna	62	20 (32.2%)	42 (67.7%)	-

MFN: Major FN

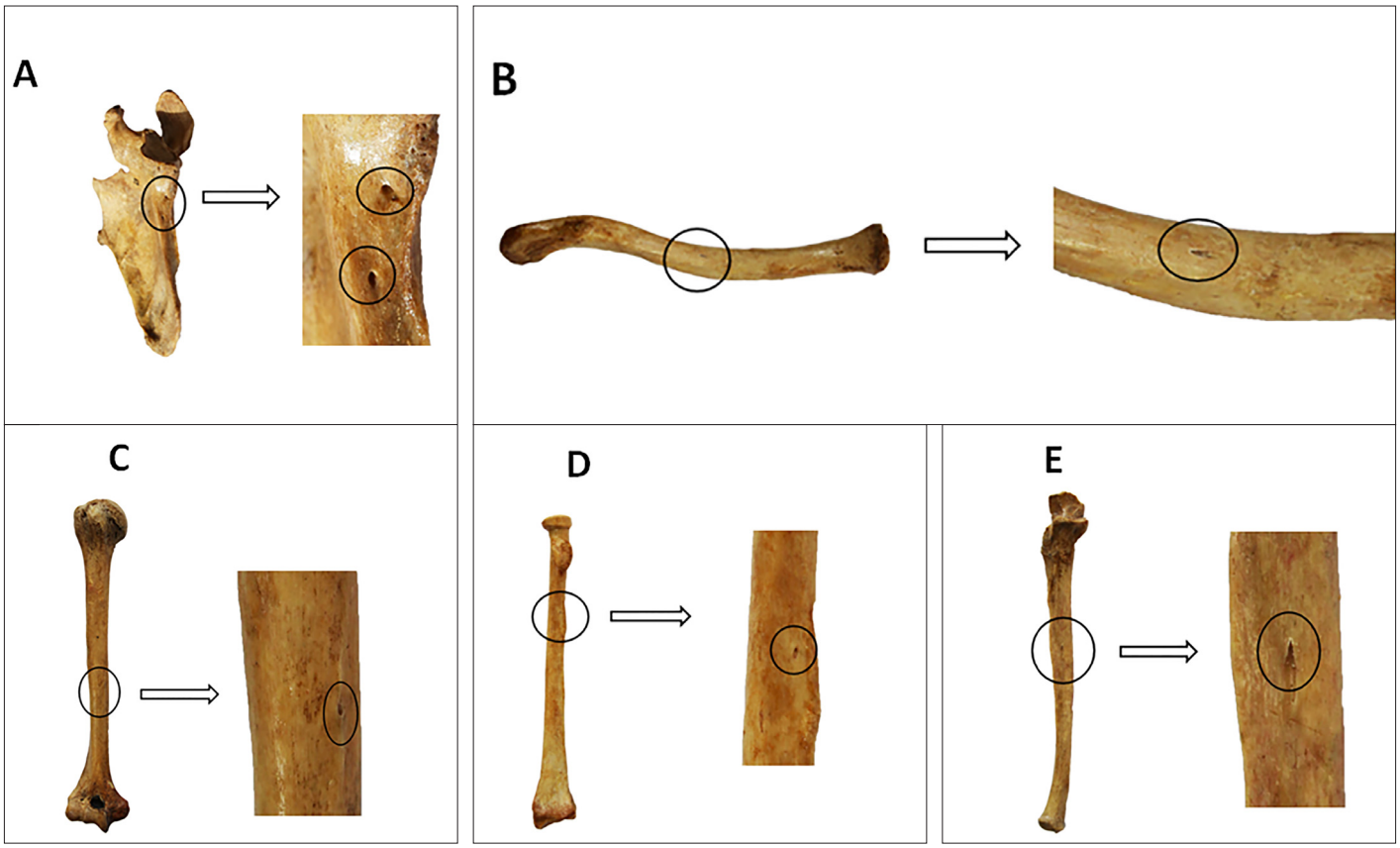

Figure 3. A-E. Determination of the FN position in relation to the bone surface (scapula, clavicle, humerus, radius and ulna respectively)

The position of the FN relative to the surfaces determined in the bone

Of the 227 FNs found in the scapula, 52 (22.9%) are in the fossa subscapularis, 43 (18.9%) are in the supraspinous fossa, 54 (23.7%) are in the infraspinous fossa, 78' i (34.3%) were found in the peri-glenoid (Figure 3A). In the clavicle, 32 (35.5%) of a total of 90 FNs were found in inferior surface, 2 (2.2%) in superior surface, and 56 (62.2%) in posterior surface (Figure 3B). Of a total of 153 FNs found in the humerus, 18 (11.7%) were found in 96 (62.7%) anteromedial surface, 9 (5.8%) in anterolateral surface, and 3 (1.9%) were seen in anterior surface and 26 (16.9%) were in posterolateral surface (Figure 3C). While 62 (65.2%) of a total of 95 FNs found in the radius were found in anterior surface, 17 (17.8%) were in anteromedial surface, and 16 (16.8%) were in anterolateral surface, FN in posterior surface was not observed (Figure 3D). While 64 (73.5%) of a total of 87 FNs found in ulna samples were observed in anterior surface, 4 (4.5%) were in anteromedial surface, and 19 (21.8%) were in anterolateral surface, it was not observed in posteromedial surface (Figure 3E).

Table 6. Comparison of literature on FN in humerus

Study	N	Number of FN						Location of FN								FI
		0	1	2	3	4	5	AS	AMS	ALS	PS	PLS	AB	MB	LB	
Ukoha et al. [4]	150	39	99	12	-	-	-	-	109	-	9	-	-	1	-	56.28
Kızılkanat et al. [9]	101	2	69	22	7	1	-	30	99	2	25	1	-	-	-	46.46
Mysorekar et al. [42]	180	-	104	69	4	2	-	-	207	-	50	-	-	-	-	-
Campos et al. [32]	36	-	27	9	-	-	-	-	36	1	7	-	-	-	-	57.73
Güner et al. [30]	50	15	33	2	-	-	-	-	31	1	3	-	-	-	-	55.7
Pereira et al. [20]	174	-	154	20	-	-	-	-	173	-	8	-	8	-	5	55.2
Solanke et al. [12]	100	4	92	4	-	-	-	-	67	-	1	-	-	32	-	-
Mansur et al. [24]	253	5	154	73	16	5	-	-	327	17	24	-	-	-	-	55.20
Ruthwik et al. [17]	80	1	50	23	6	-	-	-	43	2	14	-	2	37	1	51.50
Caroll et al. [31]	71	-	48	20	3	-	-	-	74	1	25	-	-	-	-	-
Şendemir et al. [16]	29	1	22	4	2	-	-	-	29	2	5	-	-	-	-	54.6
Öztürk et al. [23]	114	-	90	24	-	-	-	-	102	2	22	-	2	10	-	57.32
Khandve et al. [27]	80	1	77	32	-	-	-	-	44	-	4	-	3	78	-	-
Joshi et al. [28]	200	-	126	66	8	-	-	2	60	-	-	-	-	96	-	-
Present study	**103**	**7**	**59**	**24**	**8**	**3**	**2**	**3**	**96**	**9**	**18**	**26**	**-**	**-**	**-**	**55.77**

AS: Anterior surface, AMS: Anteromedial surface, ALS: Anterolateral surface, PS: Posterior surface, PLS: Posterolateral surface, AB: Anterior border, MB: Medial border, LB: Lateral border, N: number of bones, FI: Foraminal index

Table 7. Comparison of literature on FN in radius

Study	N	Number of FN				Location of FN								FI
		0	1	2	3	AS	AMS	ALS	PS	PLS	AB	MB	LB	
Ukoha et al. [4]	50	16	34	-	-	32	-	-	-	-	2	-	-	33.74
Kızılkanat et al. [9]	93	-	92	2	-	30	24	40	3	-	-	-	-	33.52
Murlimanju et al. [2]	72	3	68	1	-	-	52	-	-	-	4	10	4	34.4
Mysorekar et al. [42]	180	4	168	8	-	80	-	-	-	-	17	38	29	-
Campos et al. [32]	33	-	33	-	-	33	-	-	-	-	-	-	-	36.34
Shulman et al. [15]	164	2	161	3	-	135	-	-	-	4	-	-	25	-
Güner et al. [30]	50	12	37	1	-	33	-	-	-	-	1	2	3	35.9
Longia et al. [25]	200	-	190	8	2	194	-	-	-	-	2	6	10	-
Parmar et al. [22]	60	-	60	-	-	60	-	-	-	-	-	-	-	36
Solanke et al. [12]	80	3	77	-	-	59	-	-	-	-	1	9	8	34.36
Pereira et al. [20]	157	-	156	1	-	115	32	5	5	-	-	-	-	35.7
Akbari et al. [33]	63	-	63	-	-	52	-	-	-	1	9	-	1	36.14
Patel et al. [21]	40	-	44	-	-	44	-	-	-	-	-	-	-	38.3
Present study	**102**	**13**	**83**	**6**	**-**	**62**	**17**	**16**	**-**	**-**	**-**	**-**	**-**	**34.93**

AS: Anterior surface, AMS: Anteromedial surface, ALS: Anterolateral surface, PS: Posterior surface, PLS: Posterolateral surface, AB: Anterior border, MB: Medial border, LB: Lateral border, N: number of bones, FI: Foraminal index

Table 8. Comparison of literature on FN in ulna

Study	N	Number of FN				Location of FN								FI
		0	1	2	3	AS	AMS	ALS	PS	PLS	AB	MB	LB	
Ukoha et al. [4]	50	11	39	-	-	39	-	-	-	-	-	-	-	36.70
Kızılkanat et al. [9]	102	-	101	1	-	34	26	21	2	-	-	-	-	38.84
Shulman et al. [15]	164	1	149	14	-	136	-	-	-	-	4	-	24	-
Murlimanju et al. [2]	75	-	75	-	-	65	-	-	-	-	-	8	2	34.4
Mysorekar et al. [42]	180	2	168	10	-	137	-	-	-	-	-	32	19	-
Campos et al. [32]	33	-	30	3	-	33	-	-	-	-	-	-	-	36.81
Longia et al. [25]	200	-	190	8	2	194	-	-	-	2	-	6	10	-
Güner et al. [30]	50	9	41	-	-	38	-	-	-	-	-	2	1	38.3
Pereira et al. [20]	146	-	144	2	-	120	9	17	-	-	-	-	-	37.9
Solanke et al. [12]	80	3	77	-	-	59	-	-	-	1	-	9	8	36.52
Parmar et al. [22]	60	-	58	2	-	35	-	-	-	5	-	4	2	32.7
Priya et al. [19]	200	-	188	12	-	158	-	-	-	-	2	33	19	35.83
Patel et al. [21]	40	-	40	-	-	35	-	-	-	5	-	-	-	34.77
Kumari et al. [26]	100	3	92	10	-	71	-	-	-	-	-	18	13	36.19
Present study	**89**	**14**	**65**	**6**	**3**	**64**	**4**	**19**	**-**	**-**	**-**	**-**	**-**	**37.56**

AS: Anterior surface, AMS: Anteromedial surface, ALS: Anterolateral surface, PS: Posterior surface, PLS: Posterolateral surface, AB: Anterior border, MB: Medial border, LB: Lateral border, N: number of bones, FI: Foraminal index

Table 9. Comparison of literature on FN in clavicle

Study	N	Number of FN					Location of FN				FI
		0	1	2	3	4	AS	PS	IS	SS	
Rai et al. [5]	40	-	17	21	2	-	-	31	23	-	48.01
Murlimanju et al. [2]	52	2	20	23	7	-	-	36	29	1	44.72
Sinha et al. [13]	100	-	72	20	8	-	-	41	95	-	60.22
Hussain et al. [29]	60	-	22	30	6	2	12	66	30	-	51.41
Sinha et al. [14]	50	-	35	12	3	-	-	38	28	2	52.25
Tanna et al. [11]	50	-	21	26	3	-	-	31	30	-	49.01
Malukar et al. [8]	100	1	68	21	8	2	-	80	60	2	-
Present study	**61**	**6**	**28**	**16**	**8**	**1**	**-**	**56**	**32**	**2**	**53.65**

AS: Anterior surface, PS: Posterior surface, SS: Superior surface, IS: Inferior surface, N: number of bones, FI: Foraminal index

Directions of FN

It was seen that 242 (56.9%) of the FNs were oriented to the distal direction, and 183 of them were oriented to the proximal direction. Of 90 FNs in the clavicle, 2 (2.2%) were in the proximal direction and 88 (97.7%) were in the distal direction. 153 (100%) FN in the examined humeral samples were in the distal direction. It was observed that all 95 FNs in the radius were in the proximal direction. Only 1 (1.1%) of 87 FNs in the ulna were in the distal direction, and 86 (98.8%) were in the proximal direction.

DISCUSSION

FN, the external opening of the nutrient canal, has a specific location for each bone and may show variation. The factors that create these variations are the growth rates at both ends of the bone and the remodeling of the bone [5]. Hughes H. observed that foramen variation was most common in the femur, and rarely in the radius bone in the upper extremities, but was very rare in other bones [2]. Comparison of our study findings with the literature is given in Table 6-9 [2, 5, 8, 9, 11-33].

Nutrient artery plays an important role in the nutrition of bones by feeding 2/3 of the bone and the entire medulla. Due to the important role of FNs in the nutrition and growth of bones, the nomenclature "nutrient", which means "nutritive, high nutritional value, building material", has been made [8]. Having an important role in both prenatal and postnatal periods, a. nutricia also supports the formation of callus at the fracture site [34]. Healing of fractures depends on blood circulation as in all wounds [4]. Fractures may be accompanied by rupture of the nutrient artery. Especially in long bones, stress fractures associated with periosteal detachment, disruption of peripheral arteries, nutrient artery rupture, and soft tissue damage are also observed in such fractures [9].

In a study of the scapula, one of the bones of the shoulder girdle, Donders et al. [34] stated that the spine of scapula and the peri-glenoid are the thickest and most voluminous parts of the scapula. Therefore, they assumed that the nutrient artery provided the nutrition of these regions the most, and they reported that this assumption was consistent with their findings. The weakest point of the clavicle is the lateral 1/3 and middle 1/3 of the bone. Clavicula fractures constitute 2.6-12% of all fractures and 44-66% of shoulder-related fractures [35]. Humerus fractures are seen with a frequency of 1-7% among all fractures [36]. Thirty percent of the fractures are seen in the proximal 1/3, 60% in the middle 1/3 and 10% in the distal 1/3 [37]. Particularly proximal humerus fractures are among the most common fractures and constitute approximately 3% of upper extremity fractures [38]. Radius fractures constitute 20% of the cases with fracture development and 75% of all fractures in the forearm region [39]. Since methods such as plated osteosynthesis and intermedullary nailing can cause soft tissue damage and infection in fracture repair surgery, stabilization can be achieved with open reduction and internal fixation methods [38, 40]. In particular, open reduction is a method that requires the surgeon to pay attention to the area of FN. Avoiding a limited area containing the FN ensures a good result [41]. The circulation of bone fragments must be preserved in this type of surgical technique for a low complication rate. Therefore, orthopedic surgeons' awareness of the nutrient artery and its entry point in the bone helps in treating broken bone. With the developments in bone fixation techniques and increasing patient demands, bone fractures are treated more surgically rather than conservatively. This situation is associated with high cost and complication risks [10].

It is known that good circulation is required for free vascular bone grafting. In the humerus, the nutrient originates from the brachial artery or the deep brachial artery. The radius receives the nutrient artery from the anterior interosseus artery or the posterior interosseous artery. In the ulna, the nutrient artery originates from the ulnar artery [42, 43] Nutrient artery may also be caused by posterior interosseus artery in the radius, which may explain the FN in the posterior facies of the radius. The anterior interosseus artery is an important artery in transplantation and reconstruction to reduce the rate of pseudoarthrosis in the radius and ulna Kızılkanat et al. [37] directly related the delay in union of the bone or nonunion of the bone in the distal part of the ulna and radius of the bone after trauma, with the lack of nutrient artery entering the bone from this region. In our study, FN was not found in the distal 1/3 of the radius and ulna. "Bhatnagar et al. [44] stated that Geibel et al. reported that FN in both radius and ulna and facies posterior is not common, therefore dorsal placement of the plate should be preferred during the operative procedure." In our study, it was found that FN was most concentrated in the anterior facies in both the radius and ulna. Knowing the circulation of the bone in free vascularized bone grafts facilitates the preservation of osteocytes and osteoblasts in the graft and the healing of the graft in the new recipient [45]. Recent results confirm the hypothesis that vascularized bone graft and joint allograft survival are strongly dependent on blood circulation. The exact topography of the FN must be known to preserve the diaphyseal vascularization of the recipient in the allograft.

Limitations

Difficulties in knowing the features of dry bones such as age, sex, or race have been reported in the literature [46]. The limitation of the study is that information about the age, sex, and race the examined dry bones is not known.

CONCLUSION

Detailed knowledge of vascularization in bones has been a decisive factor for the success of new techniques in orthopedics.

This study provided additional information on the morphology and topography of FN in the shoulder girdle bones and upper extremity long bones. Determination of safe area in orthopedic surgical procedures; It will help to preserve FN, reduce complications and increase the success rate of surgical intervention. It is thought that this study will contribute to the literature in surgical procedures.

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Ethics Committee Approval: Authors declared that the ethics committee approval was not mandatory for this study and the research was conducted ac-cording to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

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Original Research

The Effect of Warning Images and Texts on Cigarette Packages on Smoking Behavior Among Healthcare Professionals

Melek Öztürk[1], Neriman Aydın[2]

[1] Kilis 7 Aralık Unıversıty, Vocationel High School Of Health Services Kilis, Turkey
[2] Gaziantep University, Faculty of Medicine Gaziantep, Turkey

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Correspondence
Melek Öztürk, PhD,
Address: Kilis 7 Aralık Unıversıty, Mehmet Sanlı, 79000, Merkez Kilis / Turkey
E-mail: melekozturk@kilis.edu.tr

This work, "The effect of pictures and text warnings on cigarette packets to the smoking behaviour: A field research on the hospital workers affiliated to the Health Ministry" produced from a master's thesis named.

ABSTRACT

Objectives: The opinion of health staff working at hospitals connected to Gaziantep Province Public Hospitals Union on the effects of warning purposed pictures and texts on cigarette packages on smoking behavior was searched.

Methods: 458 health staff participated in the research. Percentage, frequency and chi-square test were used in the data analysis**.**

Results: 42.8% of the participants were midwife nurses, 22.5% were specialist physicians, 19.9% were laboratry-anesthesia-X-ray techician and 14.8% were general practitioners. The smoking rate of the particiapants was found to be ’41.4%. The rate of the ones who want to give up smoking was determined as 52.6%. The health staff were highly affected by the united warnings on the cigarette packages (61.5%). Most of the participants think that this application may be effective in fighting smoking (43.9%). The most important factor in giving up smoking was the health problems caused due to smoking (56.5%). Prohibition of smoking in enolosed spaces was seen as the most effective method in fighting smoking. The united warnings on the cigarette packages were seen as the least effective method both among giving up smoking reasons and in fighting smoking, differences were determined among the groups according to demographic features and smoking habits ($p>0.05$). The most effective warnings were like this in order; ‘‘smoking during pregnancy gives harn to the bayb’’ (72.1%), ‘‘protect your childeren, don’t let them breathe your smoke’’ (66.8%), ‘‘smoking causes fatal lung cancer’’ (59.6%) and the least effective warnings were like this in order; ‘‘ask for help from your doctor and the closest cottage hospital to give up smoking’’ (31.7%), ‘‘health institutions help you to give up smoking’’ (38.2%) and ‘‘smokers die young’’ (41.3%).

Conclusion: As a result of this study, it was put forth that the health staff whose smoking rate is high should primarily be taken to education programs on giving up smoking and then their support should be taken to fight smoking. On smoking behavior, the content of the warnings placed on cigarette packakes shown effective for pictures and texts should be further enhanced.

Keywords: Health staff, cigarette packages, warning purposed pictures and texts.

INTRODUCTION

Tobacco use is a significant and preventable public health issue both globally and in Turkey due to its highly addictive nature and the serious negative effects of its chemicals on human health [1]. It is estimated that 100 million people died from tobacco-related products in the 20th century worldwide, and one billion people may die in the 21st century. However, the complete prevention of these deaths by eliminating tobacco use

represents an unprecedented success in the history of public health. The World Health Organization (WHO) emphasizes that the health catastrophes caused by tobacco and its products can be prevented, and therefore, efforts should be made to eliminate this problem and change the future [2].

Tobacco and tobacco products alone constitute the leading cause of death. Approximately 1.25 billion people worldwide are smokers, and about 4 million people die each year due to tobacco-related health problems. If no action is taken, it is estimated that one billion people will die in the 21st century due to smoking-related health issues [3].

According to the Global Adult Tobacco Survey Report, 16 million adults in Turkey use tobacco, and approximately 100.000 people die each year from tobacco-related diseases [4]. This mortality rate is 15-20 times higher than that of traffic accidents [1]. It is estimated that smoking-related deaths could reach 240,000 by 2030. Smoking prevalence is higher among men than women, with an estimated 12 million men and 4 million women being smokers [5]. The WHO Global Tobacco Report has reported that nearly half of tobacco users will die from tobacco-related diseases.

Tobacco use is predicted to cause more deaths in low- and middle-income countries [6].

Health professionals, as key figures in the healthcare sector, play a crucial and influential role in gaining the trust of society and reaching a broader audience [7]. Numerous studies have observed that individuals tend to emulate the behavior of physicians. Therefore, it is recommended that healthcare professionals should not smoke, and if they do, they should refrain from smoking in healthcare facilities where patients can see them Healthcare professionals are in a prime position to lead and encourage smoking cessation or prevention within the community [8, 9].

Main Points;

- This study was conducted to evaluate the success of warning images and texts placed on cigarette packages for the purpose of combating smoking, in convincing health professionals, who are always regarded as role models in preserving and promoting health, to quit smoking.

Smoking prevalence among healthcare professionals in Turkey is still relatively high, although there has been a recent decline. In a study conducted in Turkey in 2008, smoking rates; 30% in nurses, 20% in specialist physicians, 31% in general practitioners, 25% in dentists and 34% in technicians. Healthcare personnel are in a position to set an example for the society, but with the smoking rate being so high, it is inevitably necessary to question the smoking behaviors of healthcare professionals, which should be addressed first, and to take initiatives for quitting and to get their support for the community to quit smoking. Their support in smoking cessation efforts within the community is crucial. Specifically, physicians should actively engage in anti-smoking campaigns, raise awareness of the health risks associated with smoking, and take an active role in educating patients about the dangers of smoking [10].

As life expectancy increases, there is a rise in chronic diseases. Many chronic diseases are caused by preventable risk factors, with tobacco use being one of the most important. The performance of healthcare professionals in combating this significant risk factor is crucial for the preservation and improvement of health [11]. Countries with the lowest smoking rates among physicians have been the most successful in the fight against smoking, highlighting the potential for success in addressing this important and preventable public health issue [12]. To effectively combat smoking, it is important to understand the smoking status and attitudes towards smoking cessation among healthcare professionals. Tobacco use is a serious public health problem globally and at the country level, and while everyone shares the responsibility to address this issue, healthcare personnel have a special role. They can serve as role models by not smoking themselves and provide support to patients in quitting smoking. Furthermore, healthcare professionals can play a leading role in the regulation and legislation efforts aimed at tobacco control [8].

There has been an increase in anti-smoking campaigns worldwide, including in our country, in recent years. The aim of this study is to explore the knowledge, attitudes, and opinions of healthcare professionals, who have direct interaction with the community and serve as role models, regarding the written and pictorial health warnings on cigarette packages used in these campaigns.

MATERIALS AND METHODS

This is a descriptive study conducted to determine the smoking status of health professionals working in hospitals affiliated to the Gaziantep Province Public Hospitals Association, the impact of combined warnings on cigarette packages on smoking behavior, and their knowledge and attitudes about these warnings. The Survey of Health Care Professionals on the Effects of Warning Pictures and Texts on Cigarette Packs on Smoking Behavior was applied between April 15 and October 31, 2013 on health professionals working in hospitals affiliated to the Gaziantep Provincial Public Hospitals Association, and the completed questionnaires were collected by the researcher and the data set was created. Survey questions have been created through a literature search. In these surveys, questions were asked to measure the demographic characteristics of health care professionals, their smoking status, the effects of combined warnings on cigarette packs on smoking behavior, and the importance of the pictures and warning texts on cigarette packs for health care workers (Additional-1) [13-16].

The universe of the research consists of health personnel working in hospitals affiliated to the General Secretariat of Gaziantep Provincial Public Hospitals Union. The sample of the study, on the other hand, was used to determine the number of health personnel to be sampled in the study, and the Specific Sample Selection Method was used.

The sample size was calculated with the following formula.
$n= t^2pq/d^2$
(t= 1.96 for α=0.05) [17].

The sample size was calculated with the 95% confidence interval, the prevalence of smoking in 37% (84) healthcare workers, and a minimum of 358 was found. The questionnaires of 196 midwives-nurses, 103 specialist physicians, 68 general practitioners and 91 health technicians were evaluated.

The data was entered into the computer using the SPSS 18.0 statistical package program. The data was evaluated in the SPSS package program using percentages, frequencies, and chi-square tests. Additionally, to determine the variations of each item of opinion according to independent variables, "independent samples t-test" was performed based on the nature of the variable. Moreover, ANOVA was conducted to determine the variations of each item with more than two sub-categories of independent variables.

For the research, necessary permissions were obtained from the General Secretariat of the Public Hospitals Association and the ethics committee approval with the decision number 05.03.2013/92 from Gaziantep University.

RESULTS

The average age of the participating healthcare professionals was 32.30±6.78 (min: 18, max: 53). Among the participants, 62.0% were female and 38.0% were male, with 60.1% being married. Of the healthcare professionals included in the study, 40.5% were university graduates, 42.8% were nurses-midwives, 22.5% were specialist physicians, 19.9% were laboratory-anesthesia-radiology technicians, and 14.8% were general practitioners. More than half of the participants lived in the city center, and the education level of their parents was mostly primary school. 67.3% of the participants stated that their monthly income was at a moderate level. The smoking rate among the participants was found to be 41.4%, and 48.8% of healthcare professionals smoked fewer than 10 cigarettes per day. Furthermore, more than half of the participants (52.6%) expressed a desire to quit smoking, while 26.3% had no intention to quit. When asked about the smoking status of their families, it was found that fathers (41.9%) smoked the most, followed by siblings (39.7%). Among the healthcare professionals who had quit smoking, the most common reason for quitting was the emergence of health problems related to smoking (56.5%). Warning images and texts were found to be the least effective method in quitting smoking (8.7%). The study found that graphic warnings on cigarette packages influenced 62.1% of active smokers, and 43.9% reported that these warnings effectively combat smoking. The ban on smoking in enclosed spaces was considered the most effective method, with 72.4% agreement. In addition, the graphic warnings on cigarette packages were seen as the least effective method in the fight against smoking, with 44.7% agreement (Table 1).

The smoking rate among women (35.6%) was lower than that among men (51.2%), and the difference was statistically significant ($p<0.05$). Women expressed a higher desire to quit smoking (59.8%) compared to men (44.3%). Female healthcare professionals (66.9%) were more influenced by combined warnings on cigarette packages than male healthcare workers (54.3%), although the difference was not statistically significant ($p>0.05$). Both female and male healthcare professionals stated that the most effective method in influencing smoking behavior would be the ban on smoking in enclosed spaces (Table 2, Table 3, Table 4).

Although the smoking rate among university-educated healthcare professionals was lower (40.0%) compared to high school graduates (50.8%), the difference was not statistically significant (p>0.05). As a result of the research, it was determined that both high school and university-educated healthcare professionals considered the ban on smoking in enclosed spaces as a more effective method in combating smoking, while warning images and texts on cigarette packages were perceived as less effective (Table 2, Table 3, Table 4).

Among the occupational groups, general practitioners had the highest smoking rate (57.3%). Specialist physicians were found to be the least frequent smokers (31.1%), and the difference was statistically significant (p<0.05). Additionally, general practitioners consumed more cigarettes daily compared to other groups. Nurses expressed a higher willingness to quit smoking (66.7%) compared to general practitioners (33.3%), and the difference was statistically significant (p<0.05). Health technicians were found to be the least influenced by warning images and texts on cigarette packages, and the difference was statistically significant (p<0.05). All occupational groups believed that the ban on smoking in enclosed spaces would be the most effective method. Among the participants who had quit smoking, the most common reason for quitting was health problems related to smoking, while warning images and texts on cigarette packages were perceived as the least effective (Table 2, Table 3, Table 4). Both smokers, non-smokers, and those who had quit smoking stated that the most effective method in combating smoking was the ban on smoking in enclosed spaces. The most important warning messages for the participating healthcare professionals were ranked as follows: "Smoking during pregnancy harms the baby" (71.2%), "Protect your children, don't expose them to your smoke" (66.8%), and "Smoking causes deadly lung cancer" (59.6%). The least effective messages were ranked as follows: "Ask your doctor and nearest health center for help to quit smoking" (31.7%), "Health institutions can assist you in quitting smoking" (38.2%), and "Smokers die at a young age" (41.3%).

Table 1. Distribution of Participants' Demographic Variables, Smoking Status, and Opinions on Methods Used in Combating Smoking.

Variables	n	%	Variables	n	%	Variables	n	%
Gender			**Smoking Status**			**Family Smoking Status**		
Male	174	38.0	Yes	190	41.4	Father	192	41.9
Female	284	62.0	No	245	53.5	Sibling/s	182	39.7
Total	458	100.0	Quit	23	5.1	Other**	69	15.1
Marital Status			Total	458	100.0	Mother	60	13.1
Married	275	60.1	**Years of Smoking (Active smokers and Quits)**			**Smokers' Response to Combined Warning Messages on Smoking (Including Quitters)**		
Unmarried	169	36.8	Less than 5 Years	53	24.8	Impressed	131	62.1
Divorced	14	3.1	6-10 Years	80	37.6	Not Impressed	82	37.9
Total	458	100.0	11-15 Years	50	23.5	Total	213	100.0
Educational Status			16 Years and more	30	14.1	**Effectiveness of Combined Warnings in Fight Against Smoking**		
High School	62	13.7	Total	213	100.0	Yes	201	43.9
Associate Degree	105	23.1	**Number of Smoking per Day**			No	182	39.7
Undergraduate	184	40.5	10 and less	104	48.8	No Idea	75	16.4
Master's	103	22.7	11-20	66	31.0	**Effective Method in Combating Smoking*** **		
Total *	454	100.0	21 and more	43	20.2	Banning Smoking in Enclosed Spaces	332	72.4

Occupation			Total	213	100.0	Increasing Cigarette Prices	251	54.8
General Practitioner	68	14.8	Smoking Cessation Intentions of Current Smokers			Warning Images and Texts on Cigarette Packages	205	44.7
Specialist Doctor	103	22.5	Yes	100	52.6	Reasons for Quitting Smoking Among Quitters		
Nurse-Midwife	196	42.8	No	50	26.3	Health Problems Associated with Smoking	13	56.5
Laboratory-Radiology-Anesthesia Technician	91	19.9	In the Future	40	21.1	Aesthetic Concerns	4	17.4
Total	458	100.0	Total	190	100.0	Familial and Social Pressures	4	17.4
						Warning Messages on Cigarette Packages	2	8.7
						Total	23	100.0

*4 individuals did not answer the education level question.
**Represents other family members.
***Multiple options were selected.

Table 2. Distribution of Participants by Gender, Education and Occupation, and Smoking Status

Variables	**Smoking Status**								
	Yes		**No**		**Quit**		**Total**		**X^2/p**
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Gender									
Male	89	51.2	79	45.4	6	3.4	174	100.0	
Female	101	47.5	166	58.4	17	6.0	284	100.0	11.136/**0.004**
Total	190	44.8	245	53.5	23	5.0	458	100.0	
Education Level									
High School	32	50.8	26	41.3	5	7.9	63	100.0	
University	158	40.0	219	55.4	18	4.6	395	100.0	4.802/0.091
Total	190	41.5	245	53.5	23	5.0	458	100.0	
Occupation									
General Practitioner	39	57.3	28	41.2	1	1.5	68	100.0	
Specialist Physician	32	31.1	66	64.1	5	4.8	103	100.0	
Nurse-Midwife	78	39.8	106	54.1	12	6.1	196	100.0	13.839/**0.031**
Anesthesia-Laboratory-Radiology Technician	41	45.0	45	49.5	5	5.5	91	100.0	
Total	190	41.5	245	53.5	23	5.0	458	100.0	

Table 3. Distribution of Participants by Gender, Education and Occupation, and Desire to Quit Smoking

Variables	**Desire to Quit Smoking**								
	Yes		**No**		**Quit**		**Total**		**X^2/p**
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Gender									
Male	39	44.3	27	30.7	22	25.0	88	100.0	
Female	61	59.8	23	22.6	18	17.6	102	100.0	4.553/0.103
Total	100	52.6	50	26.3	40	21.1	190	100.0	

Education Level									
High School	15	46.9	7	21.9	10	31.2	32	100.0	2.431/0.279
University	85	53.8	43	27.2	30	19.0	158	100.0	
Total	100	52.6	50	26.3	40	21.1	190	100.0	
Occupation									
General Practitioner	13	33.3	14	35.9	12	30.8	39	100.0	14.021/**0.029**
Specialist Physician	16	48.5	11	33.3	6	18.2	33	100.0	
Nurse-Midwife	50	66.7	15	20.0	10	13.3	75	100.0	
Anesthesia-Laboratory-Radiology Technician	21	48.8	10	23.2	12	27.9	43	100.0	
Total	100	52.6	50	26.3	40	21.1	190	100.0	

Table 4. Distribution of Participants by Gender, Education and Occupation, and Effectiveness of Methods in Fighting Against Smoking

Variables	**Effective Methods in Smoking Control**					
	Smoking Ban in Enclosed Spaces		**Increase in Cigarette Prices**		**Warning Images and Text on Cigarette Packs**	
	n	**%**	**n**	**%**	**n**	**%**
Gender						
Male (n=174)	70	40.2	97	55.7	129	74.1
Female (n=284)	135	47.5	154	54.2	203	71.5
Total (n=458)	205	44.8	251	54.8	332	72.5
Education Level						
High School (n=62)	26	41.9	36	58.1	46	74.2
University (n=392)	177	45.2	211	53.8	284	72.4
Total (n=454)	203	44.7	247	54.4	330	72.7
Occupation						
General Practitioner (n=68)	23	33.8	36	52.9	53	77.9
Specialist Physician (n=103)	37	35.9	49	47.6	78	75.7
Nurse-Midwife (n=196)	107	54.6	116	59.2	143	72.9
Anesthesia-Laboratory-Radiology Technician (n=91)	38	41.7	50	54.9	58	63.7
Total (n=548)	205	44.7	251	54.3	332	72.5

DISCUSSION

In our study, the smoking rate among healthcare workers was found to be 41.4%. When various studies were examined, the smoking rates among healthcare workers were found to be between 36.6% and 49.3%, which is similar to the results of our study [18-20]. The high smoking rates in our study may be attributed to various factors, such as differences in socio-demographic characteristics, variations in the study environment, and the stressful working conditions of healthcare professionals. Additionally, smoking rates are higher in developing countries compared to developed countries [21]. It is believed that this factor may be related to the high prevalence of smoking.

When studies conducted on healthcare workers were examined, it was determined that they mostly smoked less than 10 cigarettes per day. In our study, nearly half of the healthcare workers smoked less than 10 cigarettes per day. This may be due to the fact that smoking a large number of cigarettes can cause health problems and they may not have time to smoke during working hours due to busy schedules.

When studies conducted on both healthcare workers and other segments of the population were examined, it was found that more than half of smokers want to quit smoking [22-24]. This rate was found to be 52.6% in our study. It is thought that

healthcare workers, due to their professions, frequently encounter individuals who have health problems caused by smoking and are aware of the prognosis of smoking-related diseases.

The motivation for people to quit smoking should come from a logical purpose for them. This often begins with recognizing and fearing the signs of health problems caused by or associated with smoking. Many studies in this field, including our own, have shown that smokers who quit smoking were mainly motivated by experiencing smoking-related health problems or having concerns about future health problems [25-27]. Based on these results, it can be said that healthcare workers are aware of the risks of smoking on health due to their professional knowledge and observations. The reason for the emergence of these results in other parts of the society can be explained by the fact that they witness the health problems that occur in smokers in their close circles. However, the number of healthcare personnel who quit smoking in our study was insufficient (n=23), so there is a limitation in interpreting the results.

In our study, the smoking rate among men was significantly higher than among women. The smoking addiction rate among men was found to be higher than among women, and when the literature was reviewed, it was seen that in many studies, men significantly smoked more than women [28-32]. The significantly higher smoking rate among men is thought to be influenced by the social environment.

While married healthcare personnel's desire to quit smoking is more concerned about having health problems, aesthetic appearance is seen as a more dominant reason for single health workers to quit smoking. It is thought that being married and having dependents who need care may influence their decision.

In our study, it was observed that the smoking rate decreased and the desire to quit smoking increased with the increase in educational level. Similar results were found in Ergeneilek's study [33]. It is possible that the education and professional lives of healthcare workers contribute to the change in these rates in favor of health professionals, as they frequently encounter the negative effects of smoking on health. In our study and in other similar studies, the smoking rate of general practitioners was found to be higher than that of specialist physicians [34, 35]. Additionally, our study found that general practitioners smoke more cigarettes daily compared to other healthcare workers. A study conducted on healthcare workers in Turkey in 2007 found that general practitioners had a higher daily consumption of 15 or more cigarettes compared to other healthcare workers. Even though the number of cigarettes smoked may vary, the fact that health care workers smoke should be an issue that should be emphasized with sensitivity.

In our study, it was observed that nurses are more willing to quit smoking than general practitioners. It is thought that this may be related to the fact that the majority of nurses are women, being mothers and displaying a more emotional behavior in this regard.

When considering variables such as gender, profession, and education level, it is evident that the most effective method in combating smoking on all variable levels is the existence of smoking bans in enclosed spaces, followed by high cigarette prices. The warning images and texts on cigarette packages were found to be the least effective method [36, 37]. Arıkan et al.'s study also found that a significant number of healthcare workers quit smoking after the ban on smoking in enclosed spaces [38].

In our study, the most effective warning messages were, in order: "Smoking during pregnancy harms the baby," "Protect your children, do not expose them to your smoke," and "Smoking causes fatal lung cancer." Most studies conducted yield similar results to our study. Although the ranking may vary in some studies, it generally shows that texts and images related to health and children are more effective. The same applies to warning texts and images that are perceived as less effective [39, 40]. The majority of healthcare workers being married and female in our study are thought to contribute to the emergence of these results. In fact, a study argues that the presence of baby pictures may make parents feel guilty and therefore motivate them to quit smoking [41].

The relationship between smoking and lung cancer is now a well-known fact in societies, and the fact that the study group consists of healthcare workers also contributes to the perceived effectiveness of this warning text.

The least effective warning texts were: "Ask your doctor and the nearest health center for help to quit smoking," "Healthcare institutions will assist you in quitting smoking," and "Smokers die at a young age." The occurrence of these results in studies conducted outside of healthcare workers can be explained by individuals witnessing healthcare workers smoking and the high

smoking rates among healthcare professionals. The similarity of our study's results with the general population suggests that this issue needs further investigation.

The limitation of the study is that it was carried out between April 15 and October 31, 2013, the research was carried out only on the health personnel working in the hospitals affiliated to the General Secretariat of the Gaziantep Provincial Public Hospitals Union, and the entire universe could not be reached.

CONCLUSION

This study was conducted to investigate the impact of warning pictures and texts on cigarette packages on the smoking behavior of healthcare professionals, as well as to evaluate their smoking status, thoughts about quitting smoking, opinions on methods that could be effective in combating smoking, and thoughts on warning pictures and texts on cigarette packages. It is crucial for healthcare professionals, who are expected to be role models in society, to demonstrate a non-smoking identity. It was observed that the smoking rates among the healthcare professionals included in the study were higher than the general population smoking rates. It has been observed that a significant majority of healthcare professionals expressed a desire to quit smoking, and the most important reason for this was the health problems associated with smoking or concerns about future health issues. The study also found that general practitioners had higher smoking rates compared to other healthcare professionals and were the least motivated group to quit smoking. When examined in terms of gender, occupation, and education level, it was understood that the most effective method in combating smoking for all healthcare professionals was the implementation of smoking bans in enclosed spaces, while the least effective method was the warning pictures and texts on cigarette packages.

Among the warning messages, the most effective ones according to healthcare professionals were "Smoking while pregnant harms your baby," "Protect your children, don't expose them to your smoke," and "Smoking causes fatal lung cancer." The least effective messages were "Ask your doctor and nearest health center for help to quit smoking," "Healthcare institutions can assist you in quitting smoking," and "Smokers die at a young age."

Based on the results obtained from our study, the following recommendations can be made:

- Healthcare professionals have an important role in smoking cessation. However, healthcare professionals with high smoking rates should first be provided with effective training on quitting smoking and reminded of their significant roles in the community in order to obtain their support in combating smoking. These trainings should be provided during school years and maintained consistently thereafter.
- Healthcare professionals who have received training on the dangers of smoking and are willing to contribute should educate the entire community about the harms of tobacco and tobacco products, starting with their colleagues in their own institutions.
- Having healthcare professionals who do not smoke, have received training on smoking cessation, and possess effective communication skills to convince the community will contribute to the success of the fight against smoking in smoking cessation clinics.
- Despite the presence of statements on cigarette packages stating that healthcare professionals and healthcare institutions can assist in smoking cessation, the reasons why healthcare professionals and the community perceive these warnings as ineffective should be further investigated.
- The high prevalence of the desire to quit smoking among healthcare professionals is a facilitating factor for smoking cessation. Healthcare professionals should be supported in this regard.
- Studies generally indicate that the highest prevalence of smoking within families is among fathers. Therefore, supporting fathers in not smoking and encouraging them to quit, if they smoke, with the awareness that they serve as role models for their children, will greatly contribute to raising a smoke-free generation.
- Getting support from women with lower smoking rates in the fight against smoking can be an effective method. Women should be supported in this regard.
- The warnings placed on cigarette packages that are perceived as less effective can be presented in different ways.
- More impactful warnings should be added to cigarette packages, and these messages should be periodically changed.
- The control of smoking bans in enclosed spaces, which is found to be the most effective method in combating smoking, should be properly implemented, and an effective mechanism for the rapid detection of violations should be developed.R

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Original Research

Suicide Risk Screening in Primary Care

Fatma Ayhan[1], Habip Balsak[2], Sinan Aslan[1]

[1] Department of Nursing, Division of Mental Health and Psychiatric Nursing, Batman University, Faculty of Health Science, Batman, Türkiye
[2] Department of Midwifery, Faculty of Health Sciences, Batman University, Batman, Türkiye

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Correspondence
Fatma Ayhan
Address: Batman University, Faculty of Health Science, Department of Nursing, Division of Mental Health and Psychiatric Nursing, 72000, Batman, Türkiye,
E-mail: f.kucuksumbul@gmail.com

ABSTRACT

Objective: The purpose of this research was to determine the general risk of suicide in the scope of primary health care services and to evaluate its relationship with hopelessness, depression, and psychological resilience.

Methods: Seven hundred twenty-five individuals presenting to primary health care services were included in this descriptive, cross-sectional study. The research data were collected using a form including the sociodemographic information form, the Suicide Probability Scale (SPS), the Beck Depression Inventory, the Beck Hopelessness Scale, and the Brief Psychological Resilience Scale, and were analyzed on SPSS software.

Results: The general SPS score was 69.49±14.65, indicating a moderate likelihood of suicide. Significant predictors of the risk of suicide by effect sizes were, and psychological resilience. Depression level was the most powerful predictor of total SPS scores, followed by hopelessness and psychological resilience.

Conclusion: Screening the risk of suicide in primary health care services is of very great importance. Evaluating the individual's history of attempted suicide, suicidal ideation, and suicide planning provides important information in assessing the likelihood of suicide.

Keywords: Suicide; Primary care; Depression; Hopelessness; Resilience

INTRODUCTION

Suicide is a global public health problem [1]. Due to its life-threatening nature and potential to lead to death and disability, attempted suicide should be dealt with as a matter of urgency in the fields of psychiatry and emergency intervention. Suicide affects all sections of society and was the fourth most common cause of deaths in the 15-29 age group in 2019. Despite its tragic effects on the individual and society, suicide is a public health problem that can be prevented through prompt, minor interventions [2]. According to WHO data, 793,000 individuals worldwide died as a result of suicide in 2016, while according to Centers for Disease Control and Prevention, 47,000 deaths due to suicide occurred in the USA in 2017, with crude suicide rates of 19.74 per 100,000 in rural areas in the USA in 2013-2015 and 12.72 per 100,000 in urban areas [3]. The equivalent rate in India is 10.6 [4]. According to Turkish Statistical Institute (TSI) data, 3406 suicides occurred in Turkey in 2019, a rate of 4.12 per 100,000. According to TSI data for Batman, where the present study was conducted, 22 individuals lost their lives due to suicide in 2019 [5].

Although risk factors in cases of suicide are usually similar, different causes may sometimes be observed in different societies. While depression and mental diseases are particularly

important as causes of suicide in high-income countries, financial problems and societal events may be more important in middle- and low-income nations [6]. Suicidal behavior is generally significantly associated with causes such as disasters, acts of violence, depression, and stress. Acts of suicide are also more common among vulnerable groups such as refugees, migrants, and the prison population [7].

Retrospective and psychological autopsy studies indicate that a detectable mental disease is present in at least 90% of all completed suicides [8]. A high risk of suicide has been shown in several psychiatric conditions such as personality disorders, schizophrenia, bipolar disorder, and post-traumatic stress disorder [9]. Traumatic events (such as death and war) combined with these diagnoses exacerbate the risk of suicide still further [10]. Several studies have shown that a hopeless mood together with the risk factors described above increase the tendency to suicide [11]. Additionally, hopelessness has been described as a significant predictor of completed suicide among psychiatric patients followed-up for 10-20 years [12].

Systematic research has shown that 80% of suicide cases presented to primary healthcare services within the previous year, and 44% within the previous month. Thirty-one percent of suicides present to mental health services in the previous year [13]. These data show that primary health care services play a critical and life-saving role in suicide risk screenings [14]. Primary health care providers identify only between 24% and 45% of young people in their care who experience emotional distress or suicidal ideation [15]. Primary health care institutions are in an ideal position to identify individuals at risk of suicide and to refer them to mental health services [16]. The purpose of this research was therefore to determine the likelihood of suicide in individuals presenting to primary health care institutions and to determine the relationship between the likelihood of suicide and hopelessness, depression, and psychological resilience.

Main Points;

- In our study, it was determined that the probability of suicide was moderate in those who applied to primary care.
- Assessment an individual's history of attempted suicide, suicidal ideation, and suicide planning provides important information in terms of suicide risk evaluation in primary health care services.
- While depression and hopelessness are risk factors for suicide; resilience is a protective factor for suicide

MATERIALS AND METHODS

Design The data in this descriptive, cross-sectional research were collected between 30.05.2022 and 15.11.2022. The research population consisted of individuals aged over 15 years presenting to family health centers in the Turkish city of Batman. Inclusion criteria were age over 15, presentation for primary health services in the province of Batman, absence of any difficulty in reading and understanding the study questions, and voluntary participation. Individuals not meeting these criteria were excluded from the research. Epi İnfo (version 7.2.4.0) software was employed to determine the sample size based on the population of the city of Batman, which was 505,849 according to TSI data [5]. Another important parameter in determining the sample was establishing the probability of suicide. Evaluations based on previous academic studies suggest that this is approximately 2-2.5% [17]. We finally aimed to include 659 individuals in the sample, with 90% confidence and a 1% margin of error (α:0.01) using the random sampling method. An additional 20% was added to this figure in the light of potential deficient and inconsistent replies, and the study was completed with 725 individuals.

Data Collection: The data in this research were collected by the authors at face-to-face interviews in a suitable area in the family health center using a form including the sociodemographic information form, the Suicide Probability Scale (SPS), the Beck Depression Inventory (BDI), the Beck Hopelessness Scale (BHS), and the Brief Psychological Resilience Scale (BPRS).

Sociodemographic Information Form: This form developed by the authors consists of 23 questions investigating age, sex, marital status, and experiences concerning daily living activities.

Suicide Probability Scale: The SPS was developed by Cull and Gill [18] and adapted into Turkish by Eskin in 1993 [19]. This four-point Likert-type scale contains 36 items. Atlı et al. performed a validation and reliability study involving a clinical sample in 2009 and showed that it can be applied in diagnosed or undiagnosed individuals [17]. Possible responses on the original version of the scale are 'never or rarely' (1), 'sometimes' (2), 'frequently' (3) and 'generally or always' (4). Possible scores range between 36 and 144, higher scores indicating a greater likelihood of suicide. The original version consists of four

factors – hopelessness (12 items), suicidal ideation (eight items), negative self-evaluation (nine items), and hostility (seven items). The SPS consists of four subscales – hopelessness, suicidal ideation, negative self-evaluation, and hostility, and yields a total scale score. Confirmatory factor analysis was applied for the structural validity in the adaptation study into Turkish, and the four-factor structure was confirmed. Cronbach alpha values at reliability analysis were .78, .94, .79, and .70, respectively, with a general Cronbach alpha value for the scale of .89. In the present study, the scale general Cronbach alpha score was 0.912. A cut-off points of 110 was determined for the scale. Scores between 0 and 24 are regarded as normal, those between 25 and 49 are considered as low risk, scores between 50 and 74 as moderate risk, and scores between 75 and 100 as high risk [18].

Beck Depression Inventory: The BDI was developed by Beck et al. [20] for the purpose of measuring the level and severity of depressive symptoms and to determine risk in the context of depression. The validity and reliability of the Turkish language version were established by Hisli [21]. The Cronbach alpha value is 0.80, while a figure of 0.934 was determined in the present study. This four-point Likert-type scale consists of 21 items scored 0, 1, 2, or 3 (min=0, max=63). Scores of 0-9 indicate minimal depression, 10-16 mild depression, 17-29 moderate depression, and 30-63 severe depression. Higher scores indicate greater experience of depressive feelings.

Beck Hopelessness Scale: The BHS is a self-report inventory developed by Beck et al. [22] to assess the severity of anxiety symptoms. The validity and reliability of the scale were confirmed by Ulusoy et al [23]. The BHS is a one-dimensional 21-item, four-point Likert-type scale, scored from 0 (not at all) to 3 (severely). Total scores range from 0 to 63, with scores of 0–7 indicating minimal anxiety, 8–15 mild anxiety, 16–25 moderate anxiety, and scores of 26-63 a severe level of anxiety. The higher scores indicate a higher level of anxiety symptoms. Scores of 0–7 indicate minimal anxiety, 8–15 mild anxiety, 16–25 moderate anxiety, and 26-63 a severe level of anxiety. Ulusoy et al. determined a Cronbach alpha of 0.93, compared to 0.91 in the present study [23]. In this study the Cronbach alpha is 0.877.

Brief Psychological Resilience Scale: The BPRS was developed by Smith et al. [24] in 2008 for the purpose of measuring individuals' psychological resilience. It was subsequently adapted into Turkish by Doğan [25]. The BPRS is a single-dimension, five-point Likert-type scale. The factor loads of the scale items range between .63 and .79. The lowest possible score on the scale is 6, and the highest possible score is 30. Higher scores indicate greater psychological resilience. The Cronbach reliability coefficient was 0.83 in the validity and reliability study and 0.752 in the present study.

Statistical Analysis

The study data were evaluated using frequency, percentage, and mean plus standard deviation descriptive methods. Normality of distribution of the scale scores was assessed using skewness and kurtosis values, with values between -1.5 and + 1.5 being regarded as normal. Relationships between normally distributed variables were analyzed using the independent sample t test and ANOVA. Predictors of the likelihood of suicide were determined using a multilinear regression model. p values lower than 0.05 were regarded as statistically significant.

Ethical Issues

Written approval for the study was granted by the Batman University Non-Interventional Clinical Research Ethical Committee (no. 2022/05-06, dated 12.05.2022). Institutional approval was granted by the provincial health directorate to which the family health centers in the research were affiliated (no. E-47960527-774.99, dated 25/05/2022). The study was performed in line with the principal of voluntary participation, written consent being obtained from individuals aged over 18, or from the legal guardians of those aged under 18.

RESULTS

The mean BHS score of the individuals taking part in the study was 7.02±5.05. Most individuals possessed minimal (248) or moderate (231) hopelessness levels. The mean BDI score was 14.49±11.33, minimal depression levels being most common (286 individuals), followed by moderate depression levels (212 individuals). The participant's mean BPRS score was 18.73±4.37, and the mean general SPS score was 69.49±14.65 (Table 1).

No significant correlation was observed between the participants' gender or marital status and total or sub-dimension SPS scores ($p>0.05$). However, a significant relationship was observed between age and total and sub-dimension SPS scores ($p<0.05$). Post-hoc analysis was applied to identify the variables from which the significance derived. This showed that this derived from mean hopelessness, hostility, and negative self-evaluation sub-dimension and total SPS scores being significantly lower in the 25-34 age group than in the other age groups ($p<0.05$). Mean

SPS suicidal ideation scores were only significantly higher in the 15-24 age group compared to the 25-34 age group ($p<0.05$). The mean suicidal ideation sub-dimension score of participants without children was significantly higher than that of those with children ($p<0.05$). No significant difference in terms of possession of children was observed in other mean total SPS or sub-dimension scores ($p>0.05$) (Table 2).

Mean SPS hopelessness and suicidal ideation sub-dimension scores varied significantly depending on education levels ($p>0.05$). Mean SPS hopelessness subscale scores were significantly higher among uneducated/elementary and middle school graduates than in both the high school and university or above education groups. Mean SPS negative self-evaluation sub-dimension scores were significantly higher among uneducated/elementary and middle school graduates compared to high school graduates, and in high school graduates compared to participants educated to university level or higher. Mean total SPS scores were significantly lower among those educated to university level or higher compared to uneducated/elementary and middle school graduates ($p<0.05$) (Table 2).

No significant relationship was observed between income status and mean suicidal ideation or hostility sub-dimension scores ($p>0.05$). Mean hopelessness and negative self-evaluation sub-dimension and total SPS scores were significantly higher in the group whose income was lower than outgoings compared to the income higher than or equal to outgoings groups. Participants with jobs or occupations registered significantly lower mean hopelessness and hostility sub-dimension and total SPS scores than those with no job or occupation ($p<0.05$) (Table 2).

Total SPS scores and hopelessness, suicidal ideation, and hostility sub-dimension scores were significantly higher in patients reporting a psychiatric disorder than in those with no psychiatric disease ($p<0.05$), although no difference was detected in terms of the negative self-evaluation SPS sub-dimension. Only negative self-evaluation scores were higher among participants with a chronic disease compared to those without ($p<0.05$), with no difference being observed between the two groups in terms of total SPS or other sub-dimension scores (Table 3).

Table 1. Descriptive statistics regarding the scales employed

Scale (n)	(Min-Max)	$\bar{X} \pm SD$
BHS Total (725)	(0-20)	7.02 ±5.05
Minimal Hopelessness (248)	(0-3)	1.71 ±0.96
Mild Hopelessness (186)	(4-8)	5.76 ±1.39
Moderate Hopelessness (231)	(9-14)	11.14 ±1.60
Severe Hopelessness (60)	(15-20)	17.01 ±1.41
BDI Total (725)	(0-60)	14.49±11.33
Minimal Depression (286)	*(0-9)*	*3.58±3.08*
Mild Depression (148)	*(10-16)*	*12.87±1.95*
Moderate Depression (212)	*(17-29)*	*22.31±3.65*
Severe Depression (79)	*(30-60)*	*36.08±5.90*
BPRS_Total (725)	(6-30)	18.73±4.37
SPS_Total (725)	(36-118)	69.49±14.65
SPS Hopelessness Sub-dimension (725)	*(12.47)*	*24.72±6.35*
SPS Suicidal Ideation Sub-dimension (725)	*(8-32)*	*11.44±3.77*
SPS Hostility Sub-dimension (725)	*(7-28)*	*11.15±3.34*
SPS Negative Self-Evaluation Sub-dimension (725)	*(9-36)*	*22.16±5.23*

Table 2. An evaluation of sociodemographic variables and mean SPS scores

Variables	SPS Hopelessness		SPS Suicidal Ideation		SPS Hostility		SPS Negative Self-Evaluation		SPS Total	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Gender										
Female (440)	24.95	6.17	11.40	3.47	11.22	3.12	22.38	5.22	69.97	14.25
Male (285)	24.37	6.61	11.49	4.20	11.04	3.66	21.83	5.24	68.76	15.25
Test value(t/p)	***1.197***	***.232***	***-.318***	***.750***	***.682***	***.495***	***1.380***	***.168***	***1.085***	***.278***
Marital Status										
Married (165)	24.15	6.72	10.93	3.99	11.06	3.72	22.39	5.48	68.55	15.62
Single (560)	24.89	6.23	11.59	3.69	11.18	3.22	22.10	5.16	69.77	14.36
Test value (t/p)	***-1.317***	***.188***	***-1.953***	***.051***	***-.384***	***.701***	***.630***	***.529***	***-.935***	***.350***
Children										
With children (131)	23.82	6.35	10.57	3.32	10.93	3.40	22.51	5.53	67.84	14.92
No children (594)	24.92	6.34	11.63	3.84	11.20	3.33	22.09	5.16	69.85	14.58
Test value (t/p)	***-1.805***	***.072***	***-2.930***	***.003****	***-.844***	***.399***	***.847***	***.397***	***-1.423***	***.155***
Age										
15-24 years[a] (464)	25.20	6.25	11.73	3.80	11.32	3.26	22.11	5.23	70.39	14.31
25-34 years[b] (189)	23.25	6.08	10.67	3.53	10.46	3.36	21.69	4.95	66.09	14.15
35 years or over[c] (72)	25.52	7.09	11.56	3.94	11.80	3.52	23.75	5.69	72.65	16.63
Test value (F/p)	***7.044***	***.001****	***5.381***	***.005****	***6.208***	***.002****	***4.105***	***.017****	***7.764***	***.000****
Post-hoc (Tukey)	***a>b c>b***		***a>b***		***a>b c>b***		***c>a c>b***		***a>b c>b***	
Education Level										
None/elementary/ middle school[a] (66)	25.86	6.12	11.74	3.40	12.34	3.69	24.75	4.93	74.71	14.19
High school[b] (120)	24.58	6.62	11.35	4.06	10.77	3.35	23.23	5.16	69.94	15.06
University or above[c] (539)	24.62	6.31	11.42	3.75	11.09	3.27	21.61	5.16	68.75	14.51
Test value (F/p)	***1.159***	***.314***	***.249***	***.780***	***5.128***	***.006****	***14.058***	***.000****	***4.975***	***.007****
Post-hoc (Tukey)	***-***		***-***		***a>b a>c***		***a>c b>c***		***a>c***	
Income Status										
Income<Outgoings[a] (273)	25.76	6.51	11.63	3.59	11.40	3.34	22.77	5.27	71.57	14.78
Income = Outgoings[b] (273)	23.63	5.80	11.18	3.83	10.91	3.19	21.64	4.85	67.38	13.67
Income>Outgoings[c] (79)	23.63	6.66	11.43	4.35	10.81	3.76	21.12	6.00	67.00	16.02
Test value (F/p)	***10.395***	***.000****	***1.132***	***.323***	***2.144***	***.118***	***5.474***	***.004****	***7.874***	***.000****
Post-hoc (Tukey)	***a>b a>c***		***-***		***-***		***a>b a>c***		***a>b a>c***	
Employment/Occupation Status										
Working/Employed (264)	23.96	6.27	11.18	3.84	10.60	3.10	21.82	4.91	67.58	14.38
Not Working/Employed (461)	25.16	6.36	11.59	3.73	11.46	3.43	22.36	5.40	70.58	14.71
Test value (t/p)	***-2.470***	***.014****	***-1.389***	***.165***	***-3.341***	***.001****	***-1.319***	***.188***	***-2.664***	***.008****

t: Independent sample t test F: One-Way Analysis of Variance (ANOVA) p: Significant Value

***p < 0.01, **p < 0.05.

Table 3. Relationships between health status and other variables and mean SPS scores

Variables	SPS Hopelessness		SPS Suicidal Ideation		SPS Hostility		SPS Negative Self-Evaluation		Total SPS	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	S.D
Psychiatric disease										
Yes (21)	30.33	8.38	15.42	6.17	13.95	4.93	24.19	5.67	83.90	16.09
No (704)	24.56	6.21	11.32	3.61	11.07	3.25	22.10	5.21	69.06	14.40
Test value (t/p)	***3.130***	***.005****	***3.030***	***.007****	***2.659***	***.015****	***1.662***	***.111***	***4.636***	***.000****
Chronic disease										
Yes (56)	26.14	6.25	11.03	3.21	11.35	3.15	24.01	5.17	72.55	14.43
No (669)	24.61	6.35	11.47	3.81	11.13	3.36	22.01	5.21	69.23	14.65
Test value (t/p)	***1.735***	***.083***	***-.840***	***.401***	***.472***	***.637***	***2.764***	***.006****	***1.627***	***.104***
Familial relationships										
Good[a] (493)	23.30	6.01	10.63	3.22	10.42	2.99	20.80	4.99	65.16	13.27
Average[b] (216)	27.67	5.81	13.01	4.17	12.53	3.37	24.94	4.46	78.17	13.00
Poor[c] (16)	29.06	8.10	14.93	5.17	15.00	4.73	26.62	5.16	85.62	13.79
Test value (F/p)	***44.038***	***.000****	***40.916***	***.000****	***45.845***	***.000****	***61.850***	***.000****	***85.107***	***.000****
Post hoc (Tukey)	***c>a b>a***		***c>b>a***		***c>b>a***		***c>b>a***		***c>b>a***	
Friend relationships										
Good[a] (448)	23.36	6.19	10.72	3.44	10.35	3.00	20.69	5.08	65.13	13.51
Average[b] (264)	26.90	5.95	12.46	3.90	12.29	3.36	24.45	4.44	76.13	13.41
Poor[c] (13)	27.53	6.66	15.23	5.05	15.61	3.92	26.46	6.52	84.84	16.83
Test value (F/p)	***29.180***	***.000****	***26.037***	***.000****	***44.811***	***.000****	***54.343***	***.000****	***63.289***	***.000****
Post hoc (Tukey)	***c>a b>a***		***a>b>c>***		***c>b>a***		***c>b>a***		***c>b>a***	
Health status										
Good[a] (324)	22.29	6.00	10.26	3.10	9.89	2.80	20.33	5.32	62.79	12.81
Average[b] (357)	26.18	5.75	12.18	3.90	11.96	3.26	23.36	4.55	73.69	13.40
Poor[c] (44)	30.86	5.81	14.04	4.40	13.86	4.02	26.00	4.96	84.77	13.09
Test value (F/p)	***62.755***	***.000****	***36.312***	***.000****	***54.745***	***.000****	***46.168***	***.000****	***90.305***	***.000****
Post hoc (Tukey)	***c>b>a***		***c>b>a***		***c>b>a***		***c>b>a***		***c>b>a***	
Regular nutrition										
Yes[a] (199)	20.78	5.21	9.89	2.73	9.29	2.55	20.54	5.52	60.51	11.65
No[b] (240)	27.79	6.49	12.92	4.23	12.67	3.45	24.12	4.87	77.51	14.38
Sometimes[c] (286)	24.90	5.42	11.27	3.52	11.17	3.07	21.65	4.81	69.01	12.92
Test value (F/p)	***81.049***	***.000****	***39.132***	***.000****	***65.808***	***.000****	***29.870***	***.000****	***91.871***	***.000****
Post hoc (Tukey)	***b>c>a***		***b>c>a***		***b>c>a***		***b>c>a***		***b>c>a***	
Sufficient rest										
Yes (344)	22.92	5.89	10.81	3.50	10.32	3.11	21.04	5.28	65.11	13.65
No (381)	26.35	6.31	12.01	3.92	11.90	3.37	23.17	4.98	73.45	14.41
Test value (t/p)	***-7.546***	***.000****	***-4.313***	***.000****	***-6.544***	***.000****	***-5.579***	***.000****	***-7.979***	***.000****

t: Independent sample t test F: One-Way Analysis of Variance (ANOVA) p: Significant Value

***p < 0.01, **p < 0.05.

Table 4. Analysis of suicidal ideation and behaviors and mean SPS scores

Variables	SPS Hopelessness		SPS Suicidal ideation		SPS Hostility		SPS Negative Self-Evaluation		Total SPS	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Previous attempted suicide										
No (701)	24.47	6.13	11.23	3.53	10.98	3.12	22.13	5.21	68.82	14.12
Yes (24)	32.20	8.12	17.41	5.41	16.12	5.29	23.25	5.93	89.00	16.80
Test value (t/p)	***6.005***	***.000****	***8.241***	***.000****	***7.696***	***.000****	***1.029***	***.304***	***6.837***	***.000****
I sometimes think about killing myself										
No (669)	24.45	6.15	11.06	3.25	10.98	3.15	22.14	5.22	68.65	14.09
Yes (56)	30.65	7.68	19.59	4.88	14.81	4.90	22.59	5.47	87.65	15.09
Test value (t/p)	***-5.506***	***.000****	***-14.096***	***.000****	***-6.506***	***.000****	***-.470***	***.639***	***-7.433***	***.000****
Have you ever thought about killing yourself?										
No (669)	24.36	6.07	11.05	3.22	10.92	3.08	22.12	5.21	68.46	13.83
Yes (56)	32.30	7.43	19.66	4.91	15.96	4.77	23.12	5.73	91.06	14.96
Test value (t/p)	***-7.255***	***.000****	***-14.557***	***.000****	***-8.912***	***.000****	***-1.070***	***.285***	***-8.502***	***.000****

***p < 0.01, **p < 0.05.

Table 5. Multilinear regression analysis of SPS scores according to BDI, BHS, and BPRS scores

	B	Sh	ß	t	p	R	R^2	F	P
BDI	0.733	0.037	0.567	19.728	.000***				
BHS	0.787	0.084	0.272	9.358	.000***	0.679	0.678	508.101	.000***
BPRS	-0.306	0.084	-0.091	-3.661	.000***				

***p < 0.01, **p < 0.05.

Hopelessness sub-dimension scores were significantly higher among participants with poor relationships with family, friends, and neighbors compared to those with moderate or good relationships (p<0.05). Suicidal ideation, hostility, and negative self-evaluation and total SPS scores were significantly higher among participants poor relationships with family, friends, and neighbors compared to those with good and moderate relationships, and among those with moderate relationships compared to the good relationships group (p<0.05). Mean total SPS and sub-dimension scores were significantly higher among participants describing their health as poor compared to those describing it as moderate or good and among those describing it as moderate compared to those with poor health (p<0.05) (Table 3).

Mean total SPS and sub-dimension scores were significantly higher among participants reporting eating regularly compared to those reporting eating regularly or sometimes regularly, and among those reporting sometimes eating regularly compared to those not eating regularly (p<0.05) Finally, mean total SPS and sub-dimension scores were significantly higher among individuals not able to devote sufficient time to resting compared to those able to rest sufficiently (p<0.05) (Table 3).

Participants who had previously attempted suicide, and those with ideations concerning suicide and how to kill themselves registered significantly higher SPS hopeless, suicidal ideation, and hostility sub-dimension and total SPS scores (p<0.05). However, these negative ideations and behaviors caused no difference in the mean negative self-evaluation sub-dimension (Table 4).

Statistically significant results were obtained in the multilinear regression model established with mean BDI, BHS, and BPRS scores as predictors of SPS scores (F: 508.101; p:0.000). The

three variables together explained 67.8% of the variance in mean SPS scores. Each also emerged as a significant predictor of SPS when the three were analyzed individually ($p<0.05$). BDI exhibited the highest predictive level (ß:0.567), followed by BHS (ß:0.272), and BPRS (ß:-0.091) (Table 5).

DISCUSSION

Approximately 80% of suicide cases have been reported to present to primary health care services within the preceding year, a finding that reveals the importance of suicide screening in primary health institutions [16]. The mean general SPS score in the present study was 69.49±14.65, indicating a moderate probability of suicide in primary presentations. Research from Turkey involving individuals diagnosed with psychiatric diseases revealed a mean SPS score of 70.97±12.82, a figure close to the value in the present research [26]. Another study from Turkey reported a mean SPS score of 71.03±15.85 in individuals diagnosed with a psychiatric disease, compared to 60.86±11.13 in those with no such disease [17].

No significant relationship was determined between gender and SPS scores in this study. Analysis of deaths from suicide in 2019 in the province where this research was conducted showed that gender rates were very similar to one another (male 22, female 18) [5]. Studies investigating the relationship between suicide and gender report that males are at greater risk [27, 28]. However, there are also studies reporting more attempted suicides among women. Research reported that 9.2% of women and 3.6% of men presenting to primary health services in India had previously attempted suicide. A retrospective study performed in an emergency department also reported that women were at a greater risk of suicide [29]. Another aspect of the association between suicide and gender is that the risk of attempts being successful is 2.83-fold higher in men than in women [11]. It should also be remembered in suicide risk assessment that men may be less likely to mention their suicidal ideations [30].

No significant association was observed in this study between the participants' marital status and their SPS scores. Marriage provides some degree of protection against suicide [31], although a marriage involving a high rate of conflict or violence can also act as a risk factor for suicide [32]. It is therefore misleading to regard being married as a protective factor against suicide.

Total SPS and sub-dimension scores were generally significantly lower among participants in the 25-34 aged group compared to those aged 15-24 or 35 and over. Negative self-evaluation scores were higher in the 35 and over age group compared to the other groups. One study involving TSI suicide data for 2007-2016 reported that suicides were most frequent in the 20-24 age range, but also increased with age after 35 [33]. Suicide is an one of the most frequent causes deaths among young people and adolescents [34]. In addition, records show that the most common age for suicides in Turkey is 20-24 [5]. Our results are consistent with the previous literature and confirm that young people and adolescents are particularly vulnerable in terms of the risk of suicide. In addition, the significant elevation in negative self-evaluation scores among individuals over 35 in the present study shows that such self-evaluation increases with age. This suggests that age-dependent feelings of inadequacy and negative ideation may be associated with an increased risk of suicide.

Participants without children in this study registered significantly higher SPS suicidal ideation sub-dimension scores than those with children. Previous studies have also identified having children as a protective factor against suicide [27, 35]. Interestingly, although possession of children is a protective factor against suicide and attempted suicide, stress associated with bringing up children can also increase the risk of suicide [34].

Total SPS and hostility and negative self-evaluation sub-dimension scores increased as participants' education levels decreased. No relationship was determined between education level and mean SPS hopelessness and suicidal ideation scores. The higher likelihood of suicide attempts resulting in death or severe injury in individuals with low education levels supports our finding [11]. It is important to bear in mind the association between a high level of education and economic status when assessing the risk of suicide. This should also be evaluated in terms of individuals with a high level of education also enjoying better economic status.

Individuals with low levels of income in this research registered lower total SPS and hopelessness, hostility, and negative self-evaluation sub-dimension scores than those with moderate and high incomes. Individuals with jobs or occupations had lower total SPS and hopelessness, and hostility sub-dimension scores than those with no job or occupation. These findings show that a low economic status and income increase the risk of suicide. It should be noted that, since public awareness and knowledge

of individuals having an academic education, a lower mortality rate because of suicide is seen as low educational status may result in inadequate job opportunities, economic problems, inefficient coping styles with problems and addiction; all these can worsen consequences in suicide [11].

While participants reporting a psychiatric disorder registered higher total SPS and hopelessness, suicidal ideation, and hostility sub-dimensions scores than those with no psychiatric disorder, no difference was found between the two groups in terms of negative self-evaluation sub-dimension scores. Retrospective and psychological autopsy studies show that a diagnosable mental disease is present in at least 90% of all completed suicides [8]. Evidence from a 10-year prospective study evaluating suicidal ideation, and suicide plans and attempts revealed that the total number of psychiatric disorders emerging at the same time is a more consistent predictor of subsequent suicidal behavior than the type of psychiatric disorder involved [9].

Only SPS negative self-evaluation scores were higher among participants with a chronic disease than in those with no such disease. Individuals describing their health status as poor registered significantly higher total SPS and sub-dimension scores than those describing it as moderate or good. In support of these findings, one study retrospectively investigating suicide attempts among adolescents with chronic disease showed that individuals with chronic diseases were at a greater risk of both single and multiple attempts at suicide, and had a 6.14-fold greater risk of multiple attempts than healthy individuals [28]. Other research involving individuals hospitalized due to medical disease confirmed that 62.9% of individuals at risk of suicide (73/116) exhibited 'thoughts of harming oneself or of being better off dead' on PHQ-9 [36]. Determining the risk of suicide only by means of depression screening tools in inpatient units may not be sufficient to identify adult medical inpatients at risk of suicide. Direct questions about the risk of suicide and using validated tools are essential for effectively and productively screening for the risk of suicide in this population [36].

Participants with poor relationships with family, friends, and neighbors registered higher total SPS and all sub-dimension scores than those with moderate or good such relationships. Similarly, a lower risk of attempted suicide has been reported in adolescents with a combination of powerful family ties and an effective neighbor network [37]. A cross-sectional study of depressed patients with no previous history of attempted suicide determined that these felt greater responsibilities towards their children and families, feared social exclusion, were skeptical about suicide for religious reasons, and exhibited greater survival and coping skills [38]. Healthy and well developed coping skills can provide a buffer against stressful life events and reduce the likelihood of suicide [39].

Participants with regular eating habits registered higher total and sub-dimension SPS scores that those eating only sometimes regularly or irregularly. The total SPS and sub-dimension scores of participants who were able to devote sufficient time to resting were significantly higher than those of individuals who were not able to rest sufficiently. In agreement with our findings, effective health care is regarded as a protective factor against suicide [40].

Participants with histories of attempted suicide, suicidal ideation, and suicide planning registered higher total SPS and suicidal ideation, hopelessness, and hostility sub-dimensions scores, although such ideations and behavior caused no significant difference in mean negative self-evaluation scores. The most powerful risk factor for suicide is a previous history of attempted suicide [2, 41]. A five-year follow-up study showed that individuals with a single previous attempt at suicide had a 48-fold greater probability of suicide than average individuals [42]. An epidemiological study of 18,199 cases of attempted suicide conducted in Finland reported a 30% risk of repeat attempts within five years and a 10% mortality risk due to suicide [43]. A significantly greater probability of poor suicide outcomes has been shown in individuals with ideation and histories of attempted suicide [11]. Although attempted suicide is an important risk factor for future suicide, that risk is far from definite [44]. Suicide risk assessment involving a few questions such as history of attempted suicide, current suicidal ideation, and plans for suicide can be a useful guide for health care professionals in terms of a rapid evaluation in areas involving only brief stays, such as primary health services.

BDI, BHS, and BPRS emerged as significant predictors of total SPS scores in this research. BDI was the most powerful predictor of total SPS scores, followed by BHS, and BPS. The previous literature shows that major depression is a risk factor for suicide, and is responsible for 60% of suicides [36,45], although depression screening by itself does not determine the entire risk [14]. Many commonly cited risk factors for suicide, such as depression, hopelessness, psychiatric disorders, and impulsivity, are best thought of as predictors of suicidal ideation [27]. Early

diagnosis and treatment of depressive and suicidal symptoms should therefore constitute a component of suicide prevention programs [11]. There is a confirmed association between hopelessness and suicide [12,26,41]. Research investigating the relationship between trait hopelessness and suicide has revealed significant positive correlation between trait hopelessness scores and attempted suicide, while state anxiety was only positively correlated with responses to the suicidal ideation question "In the last year, have you ever felt that life is hardly worth living?" [46]. It may therefore be misleading to evaluate suicide risks using state anxiety only. Based on the findings of the present study, psychological resilience if a protective factor against the risk of suicide. In support of this finding, studies involving individuals with psychiatric diagnoses have shown that psychological resilience reduced the risk of suicide [26, 47].

Limitations

There are a number of limitations to this research. First, since it was conducted in primary health services in a single province, the results cannot be generalized to all of Turkey or to other health institutions. The second limitation was that the determination of depression, hopelessness and psychological resilience was not based on a clinical interview. Another limitation is that the risks of suicide among individuals presenting to primary health care services but refusing to take part in the study could not be determined. This limits the data concerning suicide risk in individuals who presented to primary care services and did not participate in the research. Finally, the determination of suicide risk in this research was not based on a structured clinical interview.

CONCLUSION

Assessment an individual's history of attempted suicide, suicidal ideation, and suicide planning provides important information in terms of suicide risk evaluation in primary health care services. Assessment using these three questions is both practical and can assist health care professionals in primary care to perform further evaluation of the risk of suicide or to refer the patient to a psychiatrist. The SPS is the most valid and reliable method for determining the risk of suicide and can provide detailed information in the assessment of that risk in primary health care services. Depression and hopelessness are important risk factors for suicide, for which reason suicide risk evaluation should be performed as a matter of urgency in individuals with depression or hopelessness. However, although it is important to determine depression and hopelessness in evaluating suicide risk in primary health care services, these may not be sufficient by themselves for determining that risk. Psychological resilience is a protective factor against suicide, although it is important for risk factors and protective factors to be considered as an integral whole in assessing the risk of suicide. Therefore, health professionals working in primary health care services should be trained on the importance and implementation of suicide risk assessment. In future studies to be conducted on the subject, it is recommended that patients with high suicide risk in primary health care services and referred to psychiatrists should be followed up and long-term results should be evaluated.

Ethics Commmittee Approval: Written approval for the study was granted by the Batman University Non-Interventional Clinical Research Ethical Committee (Approval Number: 2022/05-06, Dated 2022-05-12). The study was performed in line with the principal of voluntary participation, written consent being obtained from individuals aged over 18, or from the legal guardians of those aged under 18.

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All authors read and approved the final version.

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Original Research

The Effect of Weight, Smoking, Passive Smoking, Physical Activity Level and Quality of Sleep on Cognitive Status in Adults

Nilay Şahan[1], Ceyhun Türkmen[1], Tuğba Arslan[1], Meltem Yazıcı Gülay[1]

[1] Department of Occupational Therapy, Çankırı Karatekin University, Faculty of Health Sciences, Çankırı, Turkey

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Correspondence
Nilay Şahan, PhD, PT.
Address: Çankırı Karatekin University,
Faculty of Health Sciences,
Department of Occupational Therapy
Çankırı / Turkey
E-mail: nilaysahan@karatekin.edu.tr

ABSTRACT

Objective: This study was planned to investigate how the lifestyles of adults affect their cognitive control, flexibility, and cognitive failure levels.

Methods: In this cross-sectional study, 81 individuals aged between 18 and 65 without a history of severe chronic illness, communication and emotional problems were included. The demographic characteristics of all individuals were recorded. The ability of individuals to control their negative thoughts and emotions and to cope with a stressful situation was assessed by the ***Cognitive Control and Flexibility Scale***, cognitive failure status by the *Cognitive Failure Scale*, physical activity levels by the *Short Form of the International Physical Activity Questionnaire*, and sleep quality by the *Pittsburgh Sleep Quality Index*.

Results: It was observed that as the Body Mass Index of the individuals increased, cognitive failure also increased and the assessment and coping flexibility levels of individuals exposed to passive smoking were lower ($p<0.05$). It was determined that individuals with poor sleep quality had lower cognitive control scores on emotions and higher cognitive failure scores ($p<0.05$). It was determined that there was a positive and statistically significant very weak correlation between the individuals' assessment and coping flexibility level and their physical activity level ($r=0.273;p<0.05$).

Conclusion: It is clearly seen that individuals will improve their cognitive status with changes in their lifestyles in the direction of well-being. In this context, we think that it is important to conduct more extensive research on the factors affecting cognitive status and to raise public awareness in order to minimize negative situations.

Keywords: Cognitive Function, Body Weight, Smoking Habit, Physical Activity, Sleep Quality

INTRODUCTION

Cognitive control and flexibility play a fundamental role in the ability to adapt to ever-changing environmental conditions and are associated with a variety of goal-oriented behaviors such as creativity, problem-solving, multitasking, and decision making [1]. In general, cognitive control is defined as the ability to prevent information, which is not related to the target, while focusing on the information that is related to a specific target [2]. Cognitive control is frequently associated with executive functions such as functioning memory, prevention, and set-changing and it plays an effective role in flexible behavioural responses [1]. Cognitive flexibility is, however, defined as the ability to flexibly think of different opinions and alternate responses depending on the changing environmental conditions [1,3]. Individuals with cognitive flexibility have advanced skills to perceive changes and develop different strategies for anything that might occur due to new situations [1]. An error or failure that might occur in an activity, which the individual could accomplish in daily

life, is defined as cognitive failure [4]. Concentration problems, memory loss, and reduced perception prevent fulfilling the task [4,5].

Dietary habits lay the foundation of health in any period of life. The dietary habits acquired at an early age allow for improving the quality of life and protect health at later ages. Moreover, sufficient and balanced dietary habits also prevent the risk of chronic diseases that might develop such as cancer, diabetes, and hypertension [6]. Besides all these physical problems, many brain scanning and behaviour studies in the literature compared the normal weight individuals and overweight individuals and those studies reported results proving that an increase in the BMI (body mass index) had a close relationship with frontal lobe functions and white matter disorders in brain, significant intellectual and cognitive deficiencies, and increased dementia and Alzheimer's disease prevalence at advanced ages [6-8].

Smoking is another factor affecting cognitive functions. It is seen that there is no complete consistency in the studies in the literature on this subject. In some studies, emphasized that, even at low doses, smoking increased the risk of cardiovascular diseases and stroke and it had a strong biological correlation with dementia and cognitive decline [9]. However, some studies also say that the relationship between current smoking and decline in cognitive functions is less [10,11]. Another condition concerning smoking is passive smoking, defined as being unwillingly exposed to cigarette smoke [12]. In a study carried out by Argüder et al. [12], it was reported that passive smoking increased the risk of lung cancer and other cancer types and that it caused coronary heart disease, stroke, and chronic lung disease [12]. In a study systematically examining the relationship between passive smoking, cognitive disorder, and dementia, it was concluded that there were weak proofs regarding the relationship between passive smoking and cognitive disorder, but the methodological variation and inconsistency of studies prevented the achievement of absolute results [13].

Main Points;

- There are many factors influencing individuals' cognitive condition.
- Cognitive failure increases with increasing BMI level.
- Assessment and coping scores of individuals exposed to passive smoking are lower.
- Individuals having sleep disorders have lower cognitive control scores and higher cognitive failure scores.
- Individuals' assessment and coping flexibility levels increases with increasing level of physical activity.

Although it is an easy-to-accept opinion to encourage individuals to physical activity for cardiovascular and musculoskeletal system health, the field of physical activity for cognitive functions continues rapidly expanding [14]. The effects of physical activities performed during life from childhood to elderliness have been reported in previous studies [15,16]. In particular, it was proven that cognitive functions such as attention or cognitive flexibility, which are those affected by brain development the most, and cognitive functions such as memory, which are those depending on the experiences the most, are the fields that are sensitive to physical activity the most [16]. However, despite all, it is also expressed that more comprehensive studies should be carried out about how the parameters of physical activity (such as duration, intensity, etc.) should be and which cognitive functions the physical activity has effects on [17].

The effect of sleep quality on cognitive functions has been examined in many previous studies [18,19]. Degradation in sleep quality was related to degradations in cognitive functions such as concentration, decision-making, memory, etc., and job-related difficulties [18,19].

In the literature, it can be seen that previous studies examining cognitive functions mainly focused on geriatric individuals or adults having a chronic disease and that the number of studies addressing healthy adults is very limited [5,9-11,17-19]. The present study aims to investigate how the lifestyles of healthy adults affect their cognitive control and flexibility level and their cognitive failure levels.

MATERIALS AND METHODS

Subjects

The present study involved individuals aged between 18 and 65 years and having no communicational or emotional problems. Those having severe chronic disease history (diagnosis of neurologic disorder or cancer) and nonvoluntary individuals were excluded.

The present study was approved by the Scientific Research and Publication Ethics Committee of Çankırı Karatekin University (desicion date 06.28.2022 and code b36755a4f1504b23). The

study was carried out in line with the Declaration of Helsinki. Consent forms were obtained from all the participants in the study

Assessment Tools

Demographic characteristics of participants such as age, height, weight, educational level, employment status, smoking status, passive smoking status, and place of living were recorded.

Cognitive Control and Flexibility Scale (CCFS) was used in order to measure individuals' ability to control intrusive and negative thoughts and emotions and flexibly cope with a stressful situation. This scale was developed by Garbys et al. (2018) and adapted to the Turkish language by Demirtaş [20]. Consisting of 18 items in total, the scale is implemented using 7a -point Likert scale (1 = not agreed at all, 7 = completely agreed). The scale has two dimensions (Cognitive Control on Emotions and Assessment and Coping Flexibility) and Cronbach's Alpha reliability (internal consistency) coefficients of dimensions were reported to be .85 and .91. The higher scores on this scale indicate a higher assessment and coping flexibility and cognitive control on emotions [20].

The cognitive failure level of individuals was measured using the *Cognitive Failure Scale*. The Cognitive Failure Scale (CFS) has 7 items about memory, 9 items about attention deficit, 7 items about failure, and 2 items about names. Consisting of 25 items, the scale questions how frequently the cognitive conditions have been experienced in the last 6 months. During the assessment, the individuals use the suitable option in a 4-point Likert scale (Very frequent "4", frequent "3", sometimes "2", rarely "1", and never "0"). The total score ranges between 0 and 100 points. Higher scores indicate susceptibility to cognitive failure [4].

Developed by Craig, *International Physical Activity Questionnaire (UFAA) – Short Form* was used in measuring the physical activity levels of individuals [21]. The reliability and validity study in the Turkish language was carried out by Öztürk [22]. The form consists of 7 items and investigates the time spent in sitting, walking, and medium- and high-intensity activities in the last week. The total score was calculated as the sum of low-intensity physical activity (walking), medium-intensity physical activity, and intense physical activity as time (minutes) and frequency (number of days). The energy needed for the activities is calculated as the MET-min score. One MET-min/week is calculated by multiplying the number of days of activity, minutes, and MET score. Considering the assessment results, individuals are categorized by the physical activity level as inactive (not physically active, <600 MET-min/week), minimally active (low level of physical activity, 600-3000 MET-min/week), and sufficiently active (sufficient level of physical activity, >3000 MET-min/week) [22].

Sleep quality was measured using the *Pittsburgh Sleep Quality Index (PSQI)*. This scale consists of 19 items under 7 sections as subjective sleep quality, sleep onset latency, sleep time, sleep efficiency, conditions affecting the sleep, use of sleep aids, and drowsiness during the day. Items are scored between 0 and 3. Total score ranges between 0 and 21 and higher scores indicate low sleep quality [23].

Statistical Analysis

Post-hoc power analysis of the study was performed using the G* Power 3.1.9.7 program [24]. The total number of samples was 81 and, as a result of the calculations, the correlation value was found to be .669 with a 5% error margin (a= .05), the power of this study (1- β) was found to be .99.

Statistical analysis was performed using IBM Statistics SPSS v26.0 (SPSS Inc, Armonk. NY, USA). Fitness to normal distribution was tested using Kolmogorov-Smirnov Test. The variables were determined using measurements (histograms, Kolmogorov-Smirnov test). Among the descriptive statistics, mean, median, standard deviation, minimum, and maximum values were utilized.

During the correlation analyses, the correlation coefficients and statistical significance were calculated using Spearman's test for variables, at least one of which was not distributed normally. As a result of the correlation analysis performed using the absolute value of correlation coefficient, the scores between 0.00 and 0.25 were considered as very weak correlation, those between 0.26 and 0.49 as weak correlation, those between 0.50 and 0.69 as medium level correlation, those between 0.70 and 0.89 as high correlation, and those between 0.90 and 1.00 as very high correlation [25]. The lowest level of significance was set at 0.05.

RESULTS

Responses of 100 individuals were taken into analysis but 19 individuals were excluded since they did not meet the inclusion criteria. Thus, the statistical analysis was completed with the responses of 81 individuals.

The demographic characteristics of all individuals are summarized in Table 1. The median age of individuals was found to be 49 (19-65) years and the median BMI (Body Mass Index) was calculated to be 26.14 kg/m^2 (18.01-43.12). It was determined that most of the participants were female (54.32%). Besides that, it was found that the educational level of volunteers was mainly the elementary/secondary school (48.15%), that the share of employees was higher (53.09%), and that individuals were living mostly in districts (50.62%). Questioning the smoking status of individuals and if they were exposed to passive smoking, it was determined that 30 (37.04%) of individuals were smokers and 31 (38.27%) were exposed to passive smoking **(**Table 1).

Individuals' cognitive control and flexibility, cognitive failure, physical activity, and sleep quality levels

Given the results obtained from Cognitive Control and Flexibility Scale, individuals' score in Cognitive Control on Emotions was 14 at minimum and 63 at maximum and the mean score and standard deviation were found to be 36.88 ± 9.39. For Assessment and Coping Levels, the minimum score was 9, the highest score was 63, and the mean score and standard deviation were 44.09 ± 8.58. In the Cognitive Failure Scale, the lowest score was found to be 0, the highest to be 67, and the mean ± standard deviation to be 34.56±15.03.

Given the results obtained from International Physical Activity Scale, the mean scores of individuals were found to be 8689.05 ± 9596.82 (MET- min/week) for high-intensity physical activity, 1496.71 ± 767.61 for medium-intensity physical activity, and 359.70 ± 151.51 for low-level physical activity.

Given the results obtained from Pittsburg Sleep Quality Index measuring the sleep quality in detail, the mean score was found to be 1.13 ± 0.68 for sleep quality, 1.27 ± 1.03 for sleep latency, 0.6 ± 0.73 for sleep time, 0.17 ± 0.41 for usual sleep efficiency, 1.64 ± 0.71 for sleep disorders, 0.12 ± 0.45 for use of sleep aid, 0.85 ± 0.88 for daytime dysfunctionality, and 5.80 ± 2.85 for total sleep quality (Table 2).

Individuals' cognitive flexibility and control levels and cognitive failure levels by their lifestyles

Examining the cognitive conditions of individuals by their lifestyles, it was determined that there was a statistically significant difference in cognitive failure levels of individuals by their BMI values and cognitive failure increased with increasing BMI level ($p<0.05$).

From the aspect of smoking and being exposed to passive smoking, smokers had lower cognitive flexibility and control levels and higher cognitive failure levels but there was no statistically significant difference between the groups. It was also determined that there was a statistically significant difference between the assessment and coping scores of individuals ($p<0.05$) and that assessment and coping scores of individuals exposed to passive smoking were lower.

Examining the cognitive conditions of individuals by their physical activity levels, there was no statistically significant difference between the groups. However, it was also determined that cognitive flexibility and control levels of individuals increased but cognitive failure levels decreased with increasing activity levels ($p>0.05$).

Considering the results obtained from Pittsburg Sleep Quality Index, it was found that there was a statistically significant difference between individuals' cognitive control on emotions and cognitive failure levels ($p<0.05$), and that individuals having sleep disorders had lower cognitive control scores and higher cognitive failure scores. (Table 3).

Relationship between individuals' lifestyles, their cognitive control and flexibility levels, and their cognitive failure levels

A positive, statistically significant, and weak relationship was found between individuals' BMI values and cognitive failure levels ($r= 0.280$; $p<0.05$).

A positive, statistically significant, and weak relationship was found between smoking and passive smoking ($r= 0.343$; $p<0.05$).
The level of cognitive control on emotions was found to have a positive, significant, and weak relationship with assessment and coping level ($r= 0.304$; $p<0.001$) and negative, significant, and weak relationships with cognitive failure ($r=-0.487$; $p<0.001$) and sleep quality ($r=-0.344$; $p<0.001$).
A positive, statistically significant, and very weak relationship was found between assessment and coping level and physical activity level; it was determined that individuals' assessment and coping flexibility levels increased with increasing levels of physical activity ($r=0.273$; $p<0.05$).
Finally, it was determined that there was a positive, statistically significant, and weak relationship between individuals' cognitive failure levels and their sleep quality levels; cognitive failure level increased with decreasing sleep quality ($r= 0.477$; $p<0.001$) (Table 4)

Table 1. Demographic Characteristics of Individuals

		N= 81
Age (year)		45 (19-65)
BMI (kg/m$^{2)}$		26.14 (18.01-43.12)
Gender	Female	44 (54.32%)
	Male	37 (45.68%)
Education	Lettered	5 (6.17%)
	Elementary School	39 (48.15%)
	High School	18 (22.22%)
	University	19 (23.46%)
Working Status	Working	43 (53.09%)
	Not Working	38 (46.91%)
Where Live	Village	5 (6.17%)
	Tow	41 (50.62%)
	Country	35 (43.21%)
Smoking Status	Smokers	30 (37.04%)
	Not Smokers	51 (62.96%)
Passive Smoking	Exposed to Passive Smoking	31 (38.27%)
	Not Exposed to Passive Smoking	50 (61.73%)

Data are presented as number (%) of participants or median (IQR).

Table 2. Cognitive Control and Flexibility, Cognitive Failure, Physical Activity and Sleep Quality Levels of Individuals

N= 81		**median (min.-max.)**	**x±SS**
Cognitive Control and Flexibility Scale	Cognitive Control on Emotions	36 (14-63)	36.88±9.39
	Assessment and Coping Flexibility	46 (9-63)	44.09±8.58
Cognitive Failure Scale		34 (0-67)	34.56±15.03
International Physical Activity Questionnaire (UFAA) – Short Form	High-intensity Physical Activity (n=20)	4531.5 (3012-37.170)	8689.05±9596.82
	Medium-intensity Physical Activity (n=39)	1221 (840-2812)	1496.71±767.61
	Low-intensity Physical Activity (n=22)	357 (132-591)	359.70±151.51
Pitssburg Sleep Quality Index (PSQI)	Sleep Quality	1 (0-3)	1.13±0.68
	Sleep Onset Latency	1 (0-5)	1.27±1.03
	Sleep Time	0 (0-3)	0.6±0.73
	Sleep Efficiency	0 (0-2)	0.17±0.41
	Sleep Disorders	2 (0-4)	1.64±0.71
	Use of Sleep Aid	0 (0-3)	0.12±0.45
	Daytime Dysfunctionality	1 (0-3)	0.85±0.88
	Total Sleep Quality	5 (1-15)	5.80±2.85

Data are presented as median.

Table 3. Cognitive Flexibility and Control Levels and Cognitive Failure Levels of Individuals According to Life Styles

N= 81		Cognitive Control on Emotions		Assessment and Coping Flexibility		Cognitive Failure	
		x±SS	p	x±SS	p	x±SS	p
BMI	>25	35.60±10.15	0.525[a]	43.61±6.99	0.762[a]	44.12±15.40	**0.004[b]**
	<25	37.77±8.84		44.64±9.16		30.76±12.81	
Smoking Status	Smoker	35.60±11.90	0.163[a]	44.23±8.50	0.902[a]	38.50±14.05	0.071[b]
	Not Smoker	37.64±7.58		44.01±8.71		32.25±15.23	
Passive Smoking	Exposed to Passive Smoking	35.03±9.55	0.220[a]	41.96±7.40	**0.028[a]**	37.25±12.89	0.207[b]
	Not Exposed to Passive Smoking	38.04±9.20		45.42±9.05		32.90±16.11	
International Physical Activity Questionnaire (UFAA) – Short Form	High	37.73±10.07	0.867[c]	46.56±6.05	0.498[c]	34.93±14.80	0.462[d]
	Medium	36.34±9.61		42.87±8.09		36.95±16.69	
	Low	34.93±10.25		42.13±8.72		37.06±13.57	
Pitssburg Sleep Quality Index (PSQI)	>5	34.20±7.82	**0.001[a]**	43.29±8.94	0.082[a]	38.27±14.06	**0.001[b]**
	<5	42.25±10.09		45.70±7.71		27.14±14.35	

BMI: Body Mass Index, a: Mann-Whitney U Test, b: Student t Test, c: Kruiskal Wallis Test, d: One Way Anova, p<0.05

Table 4. The Relationship Between Individuals' Life Styles and Cognitive Flexibility and Control Levels and Cognitive Failure Levels

	Cognitive Control on Emotions		Assessment and Coping Flexibility		Cognitive Failure		Physical Activity Levels		Pitssburg Sleep Quality	
	r	p	r	p	r	p	r	p	r	p
BMI	-0.149	0.185	-0.003	0.981	**0.280***	0.011	-0.067	0.463	-0.010	0.335
Smoking Status	-0.156	0.164	-0.014	0.903	0.211	0.058	-0.137	0.207	0.160	0.154
Passive Smoking	-0.137	0.222	**-0.245***	**0.028**	0.151	0.178	-0.140	0.195	0.120	0.284
Cognitive Control on Emotions			**0.304****	**0.006**	**-0.487****	**0.001**	0.039	0.983	**-0.344****	**0.002**
Assessment and Coping Flexibility					-0.121	0.282	**0.273***	**0.022**	-0.111	0.323
Cognitive Failure							0.036	0.595	**0.477****	**0.001**
Physical Activity Levels									-0.088	0.572

BMI: Body Mass Index, Spearman test, *p<0.05, **p<0.01

DISCUSSION

The present study aims to investigate how adults' lifestyles affect their cognitive flexibility and control levels and cognitive failure levels. During this study, the most exciting results were that overweight individuals and those having low sleep quality had higher cognitive failure levels, that individuals subjected to passive smoking had a lower assessment and coping flexibility scores, and that individuals with low sleep quality had low cognitive control levels. Moreover, there was a positive relationship between physical activity level and assessment and coping flexibility.

Nowadays, it is known that lifestyle factors such as diet, smoking, and exercise affect health and that morbidity and mortality in chronic diseases could be significantly decreased by lifestyle changes [26]. Cognitive functionality, which is a factor influencing the health perception, might influence an individual's quality of life, even their ability to live independently [27].

The prevalence of weight problems increases throughout the world. There is an increasing number of findings proving that high body mass index is related with frontal lobe dysfunction and cognitive disorders [28]. In a study carried out by Sellaro and Colzato on this subject, similar to the design of this study, university students were categorized into two groups as normal weight individuals and overweight individuals; they concluded that overweight students had a higher level of cognitive failures [28]. In the present study, when questioning if being overweight affected the cognitive functionality, it was determined that overweight individuals had higher cognitive failure levels and that, in parallel with the literature, there was a statistically significant relationship between cognitive failure level and body weight.

Smoking, one of the habits of individuals, has many important effects on health. However, despite all evidence, tobacco consumption continues around the world. In previous studies, it was reported that smoking has a clear relationship with cognitive dysfunctions and dementia [9-11]. Moreover, even though the benefit of quitting smoking at any time has been stated, it is also emphasized that it is important to quit smoking at middle age to reduce the dementia risk since the risk of dementia is related to the time after quitting smoking [9-11]. Another important result developing due to common smoking is passive smoking. In a study carried out by He et al. on elderly people, it was reported that cognitive disorder was at a higher level among individuals, who didn't smoke but tobacco was consumed in their living environment [29]. In another study carried out with adults, it was reported that there were remarkable declines in cognitive functions' processing speed among adults, who had never smoked but been exposed to cigarette smoke, especially in executive functions such as problem-solving, memory, and cognitive flexibility [30]. However, in a systematic analysis examining the relationship between passive smoking and cognitive disorder, it was determined that most of the studies reported that passive smoking had a weak relationship with cognitive disorder and dementia. Considering the results achieved here regarding both smoking and passive smoking, it can be stated that the cognitive control and flexibility levels of smokers were low, that their level of cognitive disorder was at a higher level in comparison to non-smoker individuals, and that the results were not statistically significant. In comparison to similar studies in the literature, this finding is thought to be because of the low number of participants in the present study. Given the results achieved here, it was observed that, in harmony with the literature, there was a difference in the assessment and coping levels of individuals exposed to passive smoking and there was a statistically significant difference between the two parameters.

In the literature, cross-sectional and epidemiologic studies on young and elderly adults presented evidence showing that physical activity improved cognitive functions, memory, attention processes, and executive functions [31]. Many studies showed that physical activity prevented age-related cognitive degradation, reduced dementia risk, and increased quality of life [14,16-18]. It is stated that those rehabilitative structural and functional effects were dependent upon if physical activity stimulated the blood circulation in neural circuits playing role in cognitive functions [31]. In the present study, in which physical activities of individuals were categorized as low-, medium-, and high-level and their cognitive conditions were examined in relation to their physical activity levels, it was observed that individuals' cognitive control and assessment and coping levels increased and cognitive failure levels decreased with increasing physical activity levels but the differences were not statistically significant. Considering the correlation between physical activity level and cognitive condition, it was determined that there was a statistically significant relationship between individuals' physical activity level and their assessment and coping flexibility levels. This difference in cognitive condition related to physical activity levels is consistent with the literature but it is thought that the difference was not statistically significant because the number of participants in the present study was not sufficient.

Sleep, as a regenerative mechanism, affects performance in activities requiring cognition [32]. It is stated that sleep quality affects the functioning of the brain's prefrontal cortex related to cognitive functions such as creativity, integration, and planning, and that resting, like sleep did, helped with refreshing the depleted cognitive resources [32,33]. In a large-scale study carried out on high number of young adults, the relationship between sleeplessness and daily cognitive failures was examined and it was reported that sleeplessness and low sleep quality were related with cognitive failures, especially such as attention deficit and memory [34]. In a study carried out by Stickgold and Walker [35], the authors claimed that sleep quality affected the new learning process, which is related to the brain's ability to record the newly learned task to long-term memory and causes daily cognitive failures. In sum, examining the literature, it can be seen that sleep time and quality might

mediate the relationship between cognitive failures in daily life. Consistent with the literature, the results achieved here suggest that individuals with poor sleep quality had low cognitive control on emotions and high cognitive failure levels.

The limitations of the present study include insufficient data and cross-sectional design of the study.

CONCLUSION

Health, which is considered as a multidimensional concept, is defined as the "state of wellness", beyond not being patient. In literature, the concept of wellness is generally defined as "a lifestyle, in which it is aimed to improve an individual's functionality in all physical, mental, and psychologic aspects". The most interesting point here is that the concept of wellness was defined as lifestyle. It can be seen that there are many factors influencing individuals' cognitive condition, which is a field in health that is a very comprehensive concept. According to the results of our study, it has been revealed that weight, passive smoking, physical activity level and sleep quality are associated with cognitive functions in adults. And also, it can be clearly observed that, through changes in their lifestyles, individuals could achieve improvement in their cognitive condition in form of wellness. From this aspect, in order to minimize the negative situations, the authors of this study think that more comprehensive studies should be carried out on the factors influencing the cognitive condition and that raising social awareness is very important for holistic wellness. Cognitive problems are frequently observed among elderly people. Determining the lifestyle behaviors affecting the cognitive condition of adults is very important to develop preventive strategies.

Conflicts of interest: The Authors declare that there is no conflict of interest.

Consent to participate: Consent forms were obtained from all the participants in the study.

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Author Contributions (Roles)

Nilay Şahan: design, data collection, analysis and interpretation of data, literature research, writing the manuscript
Ceyhun Türkmen: data collection, analysis and interpretation of data, literature research, writing the manuscript
Tuğba Arslan: data collection, interpretation of data, literature research, writing the manuscript
Meltem Yazıcı Gülay: data collection, interpretation of data, literature research, writing the manuscript

Ethics Approval: The present study was approved by the Scientific Research and Publication Ethics Committee of Çankırı Karatekin University (decision date 06.28.2022 and code b36755a4f1504b23). This study was performed in line with the principles of the Declaration of Helsinki.

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Original Research

The 50 Most-Cited Articles on Polyetheretherketone (PEEK): A Bibliometric Analysis

Gülbahar Erdinç[1]

[1] Department of Prosthodontics, Faculty of Dentistry, Karabük University, Karabük, Turkey

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Correspondence
Gülbahar Erdinç, DDS
Address: Department of Prosthodontics, Faculty of Dentistry, Karabük University, Karabük, Turkey
E-mail: gbaharerdinc@gmail.com

ABSTRACT

Objectives: The aim of this study was to perform a bibliometric and visualized analysis to identify and critically assess the 50 most highly cited articles on polyetheretherketone (PEEK).

Methods: The electronic search was made to identify detailed literature sources using the Clarivate-owned Web of Science (WoS) database. The terms used in the literature search are "polyetheretherketone", "poly ether ether ketone" and "peek". All articles from the search results were ranked according to citation counts, and the 50 articles that received the most citations were selected. The results were summarized and processed in a spreadsheet.

Results: 380 articles were displayed due to the search, and 50 of the most cited articles were included in the present study. Schilmidin and Stawarczyk, who have 12 papers and 974 citations, were identified as the most productive and influential researchers with equal citations and publications. Dental Materials (26%) has the highest number of publications, and Germany was determined as the most productive country.

Conclusion: Considerable advancement has been made in PEEK, as demonstrated by the increase in the number of publications linked with collaboration among various authors, nations, and institutes.

Keywords: PEEK, Polyetheretherketone, Bibliometrics, Citation analysis, Web of Science

INTRODUCTION

Bibliometric analysis is a quantitative assessment method that presents data on the analysis of the number of citations received by a publication, field of study, institution, keywords, author information, country-to-country linkage, and collaborations of an article. Visual analysis to create bibliometric networks can give users an intuitive yet thorough overview of a huge amount of data [1].

The number of citations is one of the essential parts of bibliometric analysis because it points out the impact of a research publication [2]. High-cited articles will likely guide future studies and influence clinical practice [3]. Researchers can investigate updated ideas, identify popular study topics based on bibliometric data, and collaborate with authors [4]. Authors can make inferences about the prestige and influence of journals from these analyses and benefit from these bibliometric analyses in choosing journals for future studies [1].

Polyetheretherketone (PEEK) is a linear, semi-crystalline, thermoplastic, and synthetic polymeric material used as an orthopedic biomaterial for many years [5,6]. PEEK has a lower Young's (elastic) modulus (3-4 GPa), being close to human bone, making it quite convenient for orthopedics implant application [7]. The tensile properties of PEEK are similar to those of bone, enamel, and dentin, making it a proper restorative material as far as the mechanical features are also concerned in dentistry [6–8].

PEEK has white color and superior physical properties; hence it has been appropriated for dental implant abutments, occlusal splints, and fixed and removable prostheses [6–9]. It can also be used in braces in orthodontic treatments with its aesthetic appearance [10]. Considering mechanical characteristics, chemical stability, low plaque affinity, good wear resistance, and appropriate bonding to composites and teeth, a PEEK fixed partial denture would be expected to have a reasonable survival rate [6]. The grayish appearance of metal frameworks can be eliminated due to the PEEK substructure's white color [9]. One of the significant clinical advantages of PEEK restorations is the possibility of intra-oral repair of the veneering material in chipping without restoration removal [11].

PEEK has minimal natural osteoconductive properties [12]. However, researchers show that the bioactivity of PEEK implants may improve with different methods, such as increasing its surface roughness and chemical modifications [13], coating PEEK with synthetic osteoconductive hydroxyl apatite [14] and adding bioactive particles [15]. Dental implant healing abutments and dental implants can be produced using PEEK thanks to sufficient biocompatibility [11,16].

PEEK frameworks combined with heat-cured acrylic resin denture bases and acrylic resin denture teeth may be alternatives to conventional Co-Cr frameworks [17]. PEEK has low water solubility and high chemical and thermal stability; thus, it may be a clinically appropriate choice for patients experiencing allergies to metals and more esthetic than conventionally removable partial dentures [9]. PEEK could also use as an intraradicular post in dentistry [18].

PEEK is a relatively new material, and researchers study this topic extensively. This bibliometric analysis aims to determine and review the top-cited 50 articles in PEEK and evaluate the relative importance of journals, authors, keywords, countries, and institutions.

Main Points;

- PEEK is a popular material that can be used in many areas in dentistry.
- It is the first bibliometric analysis study associated with PEEK.
- Within the search criteria, 380 articles were reached and 5 of them were evaluated.
- There are many aspects of PEEK that still need to be evaluated and it is a material open to research.

MATERIALS AND METHODS

Ethical standards were adhered to in this study. Ethical approval was not required because the study used bibliometric data from the Web of Science (WoS) database. The electronic search was made to identify detailed literature sources using the WoS database on 9 June 2023. The electronic search was limited to the topic field, which included the title, abstract, and keywords. The results were filtered as the category of the documents as dentistry oral surgery medicine. Research published in any language other than English and review articles were excluded. The terms used in the literature search are "polyetheretherketone", "polyether ether ketone" and "peek". All articles from the search results were ranked according to citation counts. Fifty articles that received the most citations were selected from 380 results, and their full text was obtained. One researcher evaluated the data extracted from WoS for inclusion and exclusion criteria three times to avoid bias. Prejudice was eliminated by evaluations made at other times, and objective results were obtained. The following bibliometric parameters of each article were recorded: article title, first author, citation count, year of publication, country, institution of publication, and study design.

The records obtained WoS were exported as a complete record in Tab Delimited File format. The cited references were processed using a bibliometric software program (VOSviewer v1.6.14.; Center for Science and Technology Studies, Leiden University). The results were summarized and processed in a spreadsheet. Data obtained by the WoS functions of "citation report" and "analyze results" were collected. VOSwiever software was used for the graphical mapping of the bibliometric material.

RESULT

Three hundred eighty articles were displayed due to the search, and 50 of the most cited articles were included in the present study. Table 1 shows the title, first author, publication year, journals, and citation of the PEEK-related first ten articles based on the WoS database. It was observed that the most cited article was the study by Schmidlin et al. [19]. Among the 50 most cited papers in the research, the article with the lowest number of citations is the articles of Schwitalla et al. [20] and Çulhaoğlu et al. [21], with 37 citations.

Table 1. The top 10 cited manuscripts according to citations

First Author	Article Title	Times Cited, All Databases	Journal ISO Abbreviation	Year
Schmidlin, PR	Effect of different surface pre-treatments and luting materials on shear bond strength to peek	156	Dent. Mater.	2010
Vandewegh, S	Accuracy of digital impressions of multiple dental implants: an in vitro study	136	Clin. Oral Implant. Res.	2017
Hahnel, S	Biofilm formation on the surface of modern implant abutment materials	138	Clin. Oral Implant. Res.	2015
Zoidis, P	The use of a modified poly-ether-ether-ketone (peek) as an alternative framework material for removable dental prostheses. A clinical report	131	J. Prosthodont.	2016
Kern, M	Influence of surface conditioning on bonding to polyetheretherketon (peek)	129	Dent. Mater.	2012
Stawarczyk, B	Peek surface treatment effects on tensile bond strength to veneering resins	113	J. Prosthet. Dent.	2014
Tannous, F	Retentive forces and fatigue resistance of thermoplastic resin clasps	123	Dent. Mater.	2012
Fuhrmann, G	Resin bonding to three types of polyaryletherketones (paeks)-durability and influence of surface conditioning	110	Dent. Mater.	2014
Koch, FP	Osseointegration of one-piece zirconia implants compared with a titanium implant of identical design: a histomorphometric study in the dog	102	Clin. Oral Implant. Res.	2010
Zhou, L	The effect of different surface treatments on the bond strength of peek composite materials	100	Dent. Mater.	2014

Figure 1 demonstrates the trend of scientific articles published related to PEEK by year of publication. According to the search made in the database after the necessary filters were selected, the oldest publication among the 50 most cited publications was from 2008 [22]. The number of articles, the journals in which they were published, and the citation relationships are shown in Figure 2. Dental Materials (26%) has the highest number of publications. It is followed by the Journal of Prosthetic Dentistry (18%), Journal of Craniomaxillofacial Surgery (12%), Journal of Prosthodontics Implant-Esthetic and Reconstructive Dentistry (%8), and Clinical Oral Implants Research (8%).

Figure 3 shows the relationship between coauthorship and the number of documents by year. Schilmidin and Stawarczyk, who have 12 papers and 974 citations, were identified as the most productive and influential researchers with equal citations and publications. As can be seen from Figure 4, when the affiliations of the authors are evaluated, the institution that produced the most articles was the University of Zurich.

Figure 5 shows the distribution of articles by country, and in this analysis, Germany is observed to be the most efficient country in producing PEEK-related publications. Figure 6 shows a mapping of the keywords used in the research included in this study. The most commonly used keywords were peek, shear bond strength, cad/cam, cranioplasty, digital impression polyetheretherketone, bond strength, and sem. When the articles included in the present study are evaluated according to study design, the results are shown in Figure 7: in vitro study (66%), case report (28%), finite element analysis (FEA) (4%) and animal study (2%).

The research topics of the articles are mainly on the bond strength of chemicals or surface treatments of PEEK. Similarly, many studies examine the physicomechanical and biological properties of PEEK, such as roughness, hardness, water absorption, fracture strength, wear resistance, bioactivity, antibacterial activity, and cytotoxicity. In addition, when the case reports are examined, using PEEK as a patient-specific implant in craniofacial defects or reconstructive surgeries comes to the fore. In addition, there are articles in which PEEK's endocrown, implant abutment, framework, clips on implants bar and clasp are produced, and their properties are investigated.

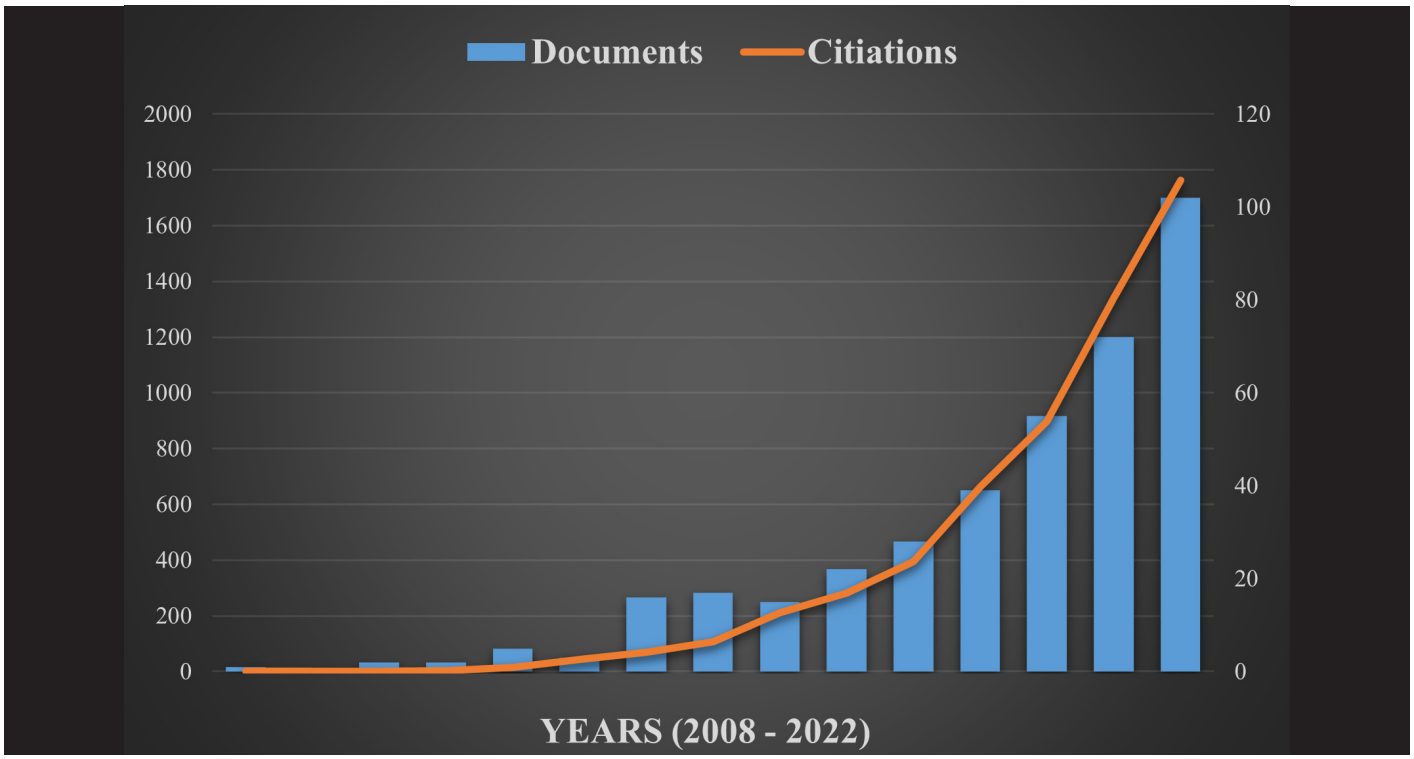

Figure 1. Distribution of articles and citations by years

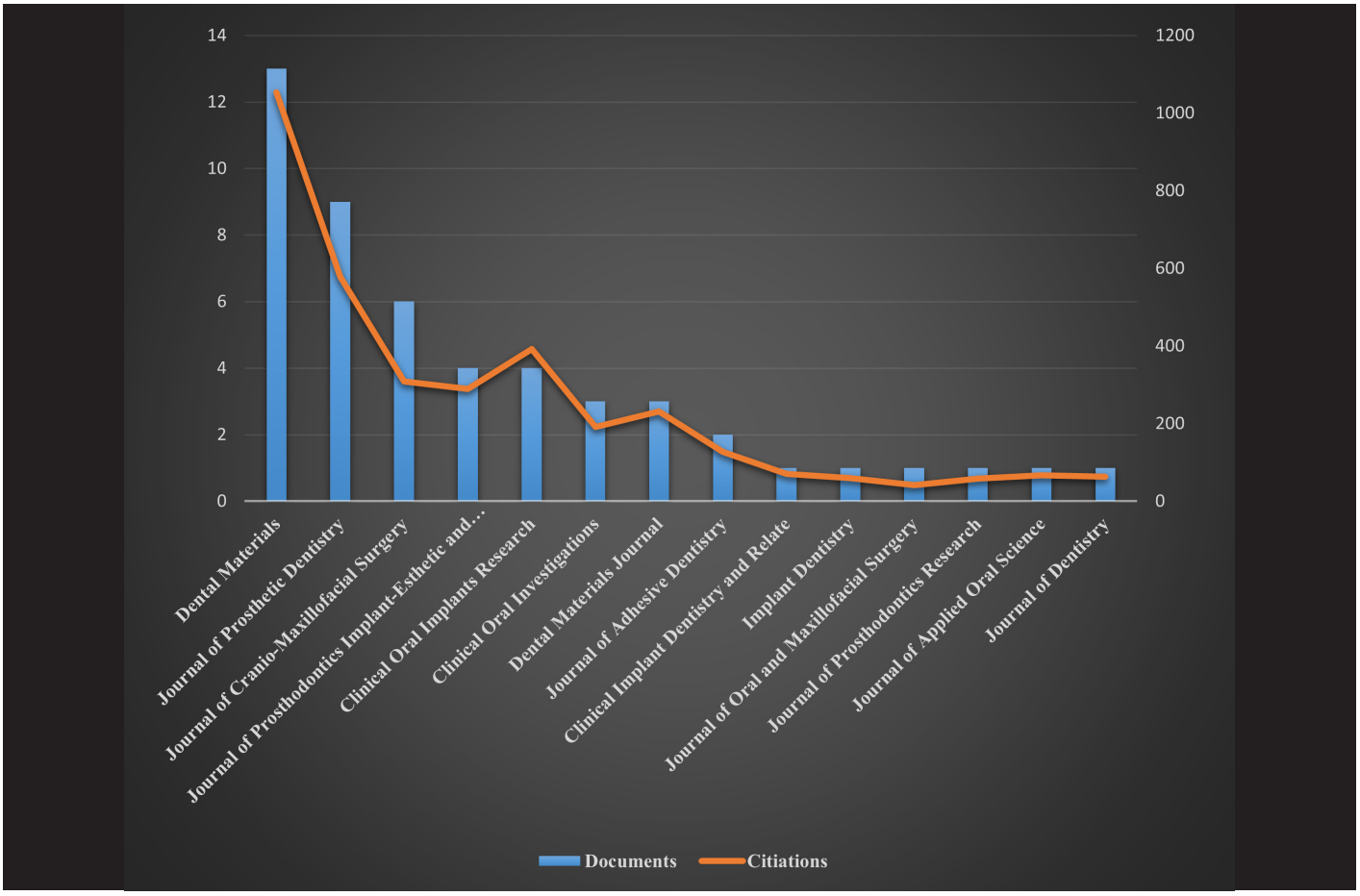

Figure 2. Distribution of articles and citations by journals

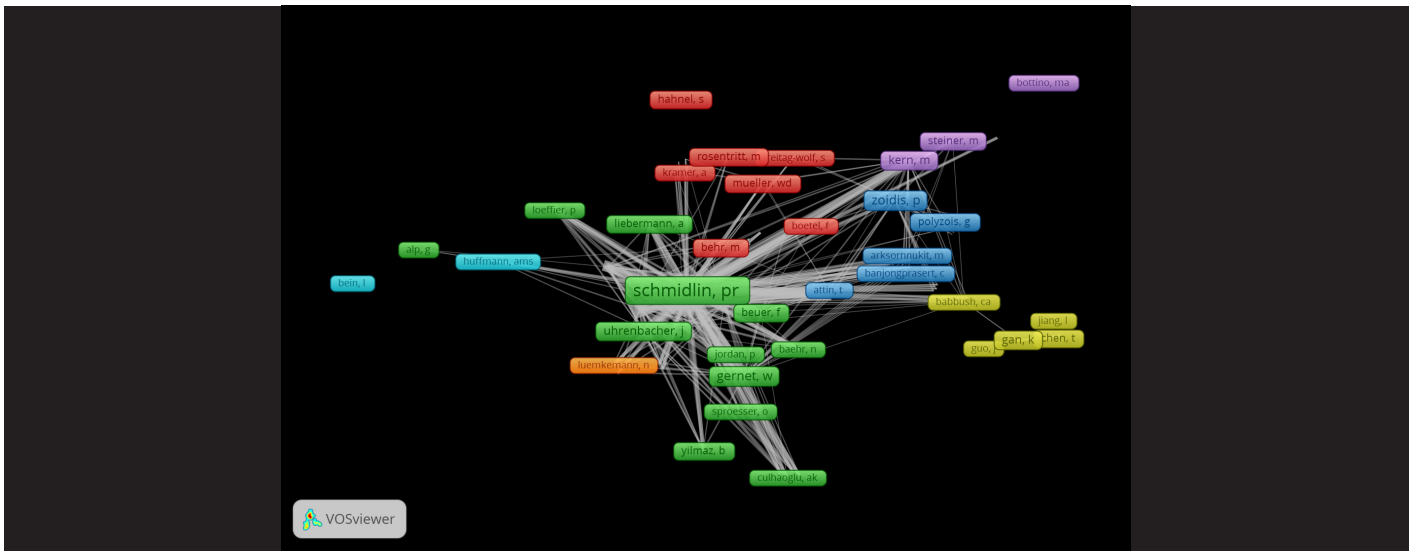

Figure 3. Collaboration networks among authors

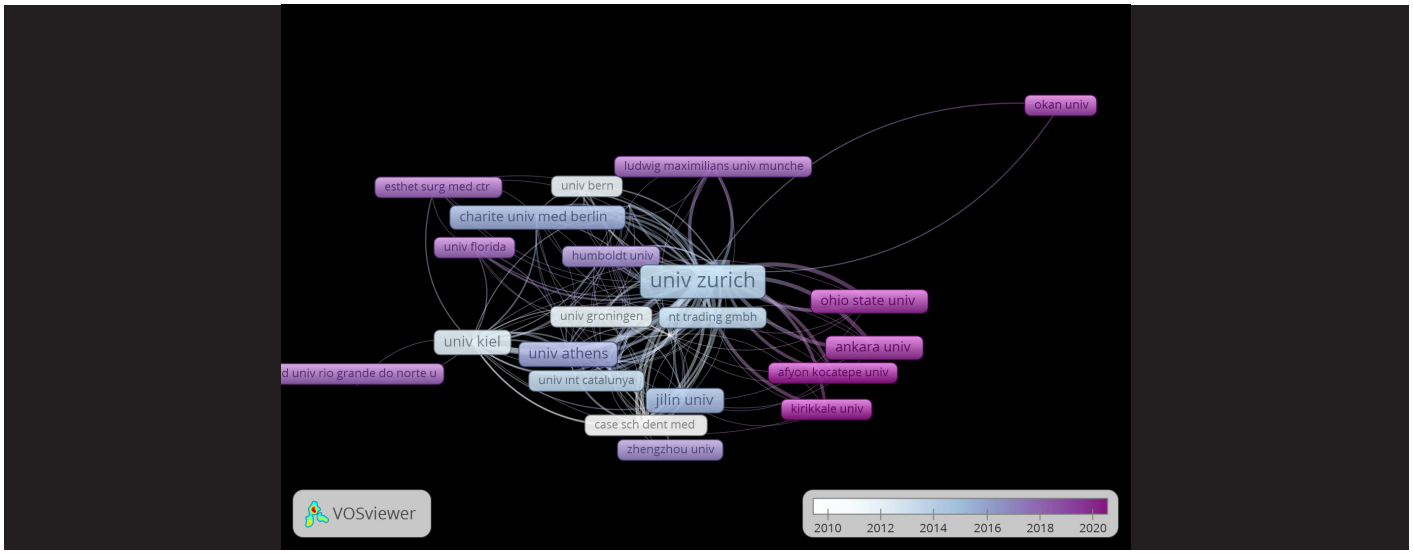

Figure 4. Affiliation of researchers by years and the number of articles they have published

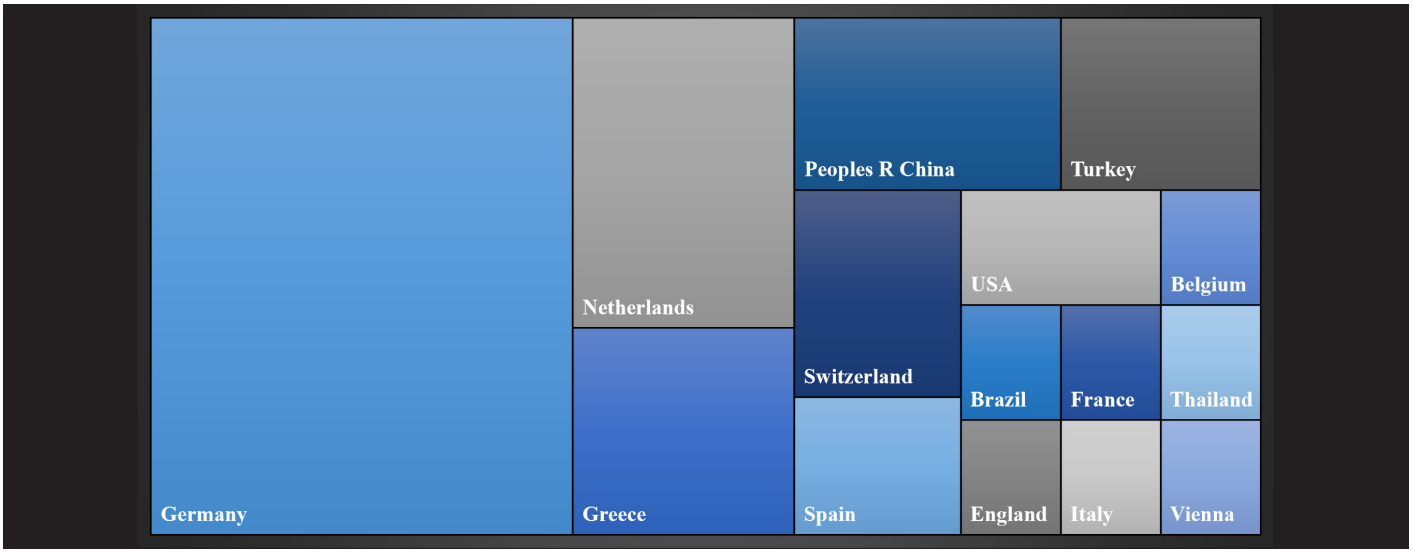

Figure 5. Distribution of published articles by country

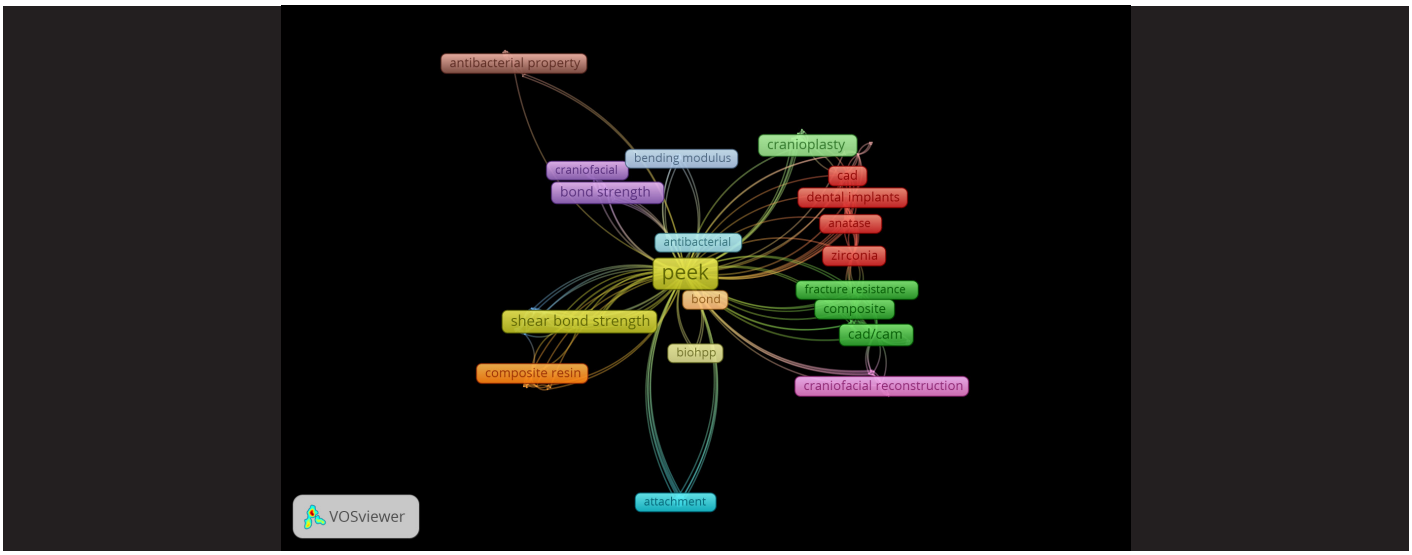

Figure 6. Commonly used keywords in articles

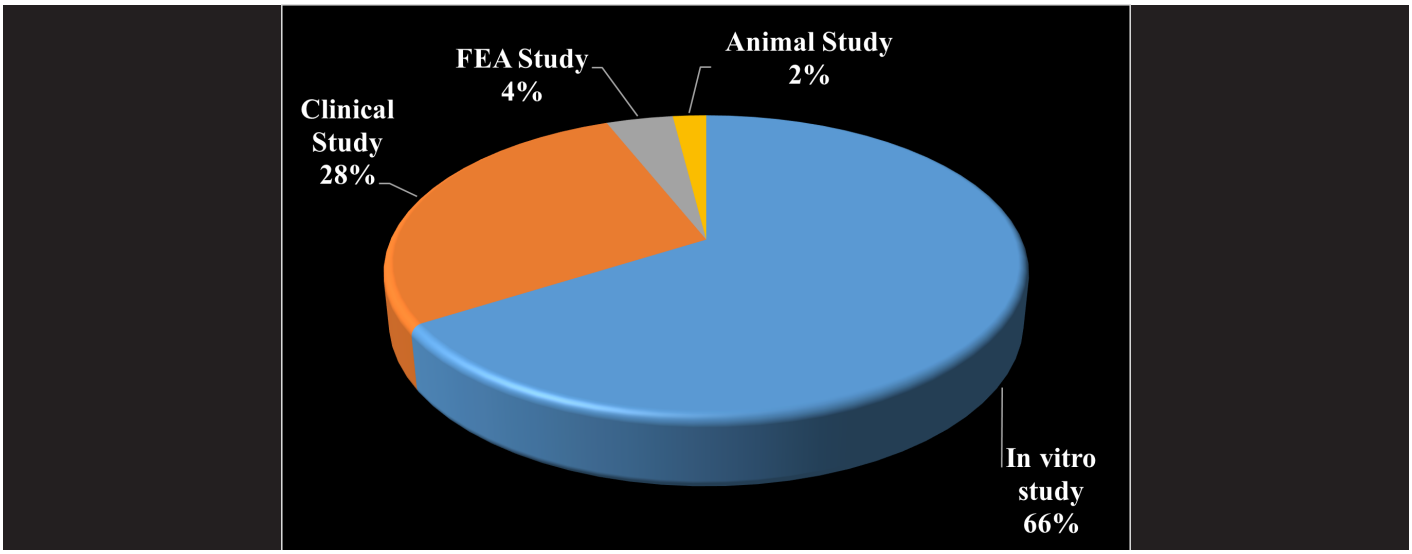

Figure 7. Distribution of published articles by study design type

DISCUSSION

This study aimed to determine and analyze the main features of the top 50 most cited articles published about PEEK. The results from the literature search showed that the number of articles on PEEK and citation count has been increasing from the past to the present. This indicates that research on this subject will become increasingly popular in the coming years.

The present study indicates that Dental Materials and Journals Prosthetic Dentistry are the two journals with the highest contribution. This situation shows that these journals are distinguished with high citation rates for publishing their PEEK research. The researchers care about journal impact factors and the suitability of these journals to the subject while choosing the appropriate journal for their academic research. Journals with higher impact factor values are given the status of being more critical or carrying more prestige in their respective fields. When similar bibliometric analysis studies in the field of dentistry are examined, especially in material research, journals such as Dental Materials, Journal of Dental Research, Journal of Dentistry, the Journal of Prosthetic Dentistry, Clinical Oral Investigations and Materials come to the fore [3,23–25].

While calculating the number of citations in this study, the Web of Science database was used as a reference, considering the existing literature studies [26,27]. The citation count for many articles is higher in Google Scholar than in WoS, which indicates that there may be changes in the citation count due to differences

in databases due to changes in the journals indexed. Ahmad et al. also reported that citation numbers fluctuate when different databases are queried, and a more specific evaluation may not be possible because Google Scholar also includes conference papers, technical reports, and theses. There is no option to sort search results according to the number of citations in Google Scholar [2].

When we evaluate the countries where the first authors originated in this study, Germany and Switzerland are at the forefront. Looking at similar bibliometric analysis studies, the USA, China, and the UK are among the countries the first authors belong to [2,3,28–30]. Countries with high citation rates are generally more economically stable. Countries with shortfalls in research facilities and socioeconomically less developed countries have contributed relatively little to this research area [3,31].

Previous bibliometric analysis studies showed that the rate of in vitro studies was higher than that of other study designs [28,30,32]. The present research results are similar to their results, and it has been determined that there are proportionally more articles with in vitro study design. This situation can be explained by the ethical problems, complications, and the risk of harming the patient, especially in using new materials in clinical studies. On the other hand, more clinical studies are needed to analyze dental materials better.

Keywords are a significant part of a research paper. While searching the literature, using keywords helps to find more relevant results. They act as "codes" to source the required scientific studies. Therefore, choosing and including keywords that can readily search and identify relevant references is imperative when researching articles. The aim of determining the most frequently used keywords was to lead researchers to search for published articles pertinent to PEEK using search engines [4].

In some articles, the search term was used as "polyetheretherketone" "polyether ether ketone" or "peek", considering that there might be a difference in spelling and to access more articles. Same way, a recent bibliometric study on regenerative endodontics used the different terms "Revitalization," "Revascularization," "Regeneration," and "Dental pulp" in order not to restrict the study results [28].

Only the Web of Science database was used in the present bibliometric analysis, which is one of the limitations of this study because no bibliometric database indexes every type of publication, and some articles may have been omitted. There are also bibliometric analysis studies in the literature using other databases such as Scopus, Medline, or PubMed. In this study, Web of Science, a reliable data source, preferred to go on a single basis [28,33,34]. The average self-citation rate in dental journals is nearly 10% [35]. Web of Science does not automatically exclude self-citations, and so this situation may be thought to be another limitation. Other limitations of this study are the inclusion of articles, books, or conference proceedings written in other languages.

CONCLUSION

The results from this present study highlight the increase and distribution of scientific production of PEEK materials from the past to now. This citation analysis gives a perspective on the progress of research in the field of PEEK and allows identification of the most significant and pertinent research areas. The predominance of in vitro studies in this research field reinforces the need for clinical studies, to extrapolate the reported features of PEEK into the clinical setting.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: The author declared that this study has received no financial support.

Ethics Committee: Ethical standards were adhered to in this study. Ethical approval was not required because the study used bibliometric data from the Web of Science (WoS) database. The electronic search was made to identify detailed literature sources using the WoS database on 9 June 2023.

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Original Research

A Comprehensive Bibliometric Analysis on Neuronavigation Researches

Ali Akar[1]

[1] Department of Neurosurgery, Çanakkale Onsekiz Mart University Faculty of Medicine, Çanakkale, Turkey

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Correspondence
Ali Akar, MD
Address: Çanakkale Onsekiz Mart University Faculted of Medicine Department of Neurosurgery, Çanakkale/Turkey
E mail: ali.akar@comu.edu.tr

ABSTRACT

Objective: Neuronavigation is a novel method that has made great advances in the field of neurosurgery. The aim of this study was to review the published literature on this topic and to investigate the current state of research and trending topics.

Methods: A bibliometric analysis of the neuronavigation on the Web of Science database was performed. The publications included in the study were analyzed with Bibliosiny, bibliometrix (version R 4.2.2), and the Literature Metrology Online Analysis Platform. Graphs from Web of Science were also utilized and some tables were created with the help of Excel.

Results: The current study included 3026 research articles on neuronavigation. 11040 authors, 2332 affiliations, and 93 countries contributed to the literature on neuronavigation. The earliest publications on neuronavigation were published in early 1990. The first article was published in Germany. The international co-authorship rate was 17.78%. Most of the international co-authorship was between the United States and Germany.

Conclusion: Neuronavigation research will remain a hot topic as technology advances. As a result, this study presented the trend and characteristics of neuronavigation studies, offering researchers a useful bibliometric analysis for future research.

Keywords: bibliometric analysis; neuronavigation; neurosurgery.

INTRODUCTION

Neuronavigation, or frameless stereotaxy, is a method that uses one of several localization procedures to locate an operating instrument in relation to the operating field without the use of a coordinate frame firmly fixed to the skulls of patients [1]. In other words, by this method, neurosurgeons can precisely locate various intracerebral disease processes with the aid of uses a variety of preoperative scans [computerized tomography (CT), magnetic resonance imaging (MRI), functional magnetic resonance imaging, positron emission tomography, single-photon emission computerized tomography, etc.] [2].

Modern neurosurgery places a significant emphasis on neuronavigation. It supports spatial orientation and enables intraoperative visualization of instruments and three-dimensional image data [3]. Only after a substantial technological advancement, particularly in the fields of informatics and imagistic, was computer-assisted surgery able to be developed [2].

Four decades after Spiegel and Wycis' successful clinical development of frame-based stereotactic neurosurgery, frameless stereotaxy was developed to allow for more complex image guidance during open neurosurgical procedures [1]. The visual pictures that are used by neuronavigation must be in three dimensions because the procedure itself is three-dimensional (3D). Since imaging technology was initially only capable of two-dimensional (2D) projection on traditional X-ray

scans, the use of neuronavigation was severely constrained. Stereotactic procedures gained enormously in popularity after the development of 3D imaging (helical CT, MRI) [2].

Roberts and Strohbehn, a surgeon and engineer group from Dartmouth (the United States), developed and first released a neuronavigation publication in 1986 [4]. It was reported that neuronavigation was first actively applied in real terms in four neurosurgical facilities in Romania in 2003 [3]. After that, as it is the simplicity, dependability, and efficiency of intraoperative stereotactic navigation in neurosurgery have all been enhanced. These developments have also made it possible for brand-new, minimally invasive neurosurgical methods to develop the properties of every neurosurgical navigation system vary [3,5]. This method enables the reduction of surgical risks and the acceleration of difficult surgical procedures. It is obvious how important it is to understand neuronavigation's accuracy and reliability given how widely available and utilized it has become. Unnoticed influences from various factors during surgery may affect the accuracy and deceive the surgeon. Every neurosurgeon must have a thorough understanding of the systems' weaknesses in addition to optimizing them as much as possible [2]. Stereotactic navigation will become more and more crucial as less invasive procedures for treating intracerebral hemorrhage such as passive catheter drainage and endoscopic evacuation gain support in the literature and become more widely used [3].

The scholarly impact of any scientific publication is frequently assessed using bibliometric analyses with different methods [6-16]. In recent years, bibliometric studies in the field of neurosurgery have started to be published at an increasing rate with the developing technological methods [17-22]. But no similar study focusing on neuronavigation research from the Web of Science database was published before. The aim of this study was to review the published literature on this topic and to investigate the current state of research and trending topics.

Main Points;

- Neuronavigation is a novel method that has made great advances in the field of neurosurgery.
- There is the first bibliometric analysis on neuronavigation research.
- Neuronavigation, frameless stereotaxy, image-guided surgery, Glioma, and Neurosurgery were among the top trend topics.
- The United States took first place with 784 articles. Germany ranked 2nd with 683 articles.

MATERIALS AND METHODS

Study Design

Ethical standards were adhered to in this study. Ethical approval was not required because the study used bibliometric data from the Web of Science database.

In this bibliometric study, a systematic search was conducted in the Web of Science Core Collection (all indexes). Firstly, the topics of articles were screened under the following terms: 'Neuronavigation* (Topic) OR Frameless stereotaxy* (Topic) were the search terms. To improve the quality of access we use the advanced search function and the search rules are defined as follows: Languages = 'All languages', Document types = 'Article', and Time range = '1990-31 December 2022'.

A total of 3026 documents from the Web of Science between 1990 and 31 December 2022 met the inclusion criteria. The dataset was downloaded as 7 separate "plain text" and "tab-delimited text files". Web of Science allows a maximum of 500 results to be downloaded at a time in "BibTeX" format and merged these 7 files.

The document types were other than research articles and the publications published before 1990 and after 31 December 2022 were excluded.

Bibliometric Analysis

The publications included in the study were uploaded to Bibliosiny, bibliometrix (version R 4.2.2) (an R tool / Biblioshiny R version 4.2.2 program [23] and the Literature Metrology Online Analysis Platform (at https://bibliometric.com/app). Graphs from Web of Science were also utilized and some tables were created with the help of Excel.

RESULTS

Main information of the articles and most productive authors/institutions and countries

The current study included 3026 research articles on neuronavigation. 11040 authors, 2332 affiliations, and 93 countries contributed to the literature on neuronavigation. English (95.737%), German (1.619%), French (1.058%), Spanish (0.463%), Japanese (0.297%), and Czech (0.264%) were mostly preferred languages by the authors. Portuguese, Polish, Chinese,

Hungarian, Italian, Russian, and Turkish also rarely publishing languages. 92.862% of the articles were published in journals indexed in the Science Citation Index Expanded index of the Web of Science core collection, also 5.188% of them Emerging Sources Citation Index.

Publications on neuronavigation were first published in early 1990. The first article was published by Roberts et al. [24] from Germany. There were 195 articles in 2021, which was the most productive year. After 2004, there was an acceleration in the number of publications (Figure 1).

A total of 58 of the publications were single-authored. The international co-authorship rate was 17.78%. Most of the international co-authorship was between the United States and Germany.

Christopher Nimsky, Professor of Neurosurgery at the University of Marburg in Germany, was the author of the largest number of publications (69 publications). In addition, Prof. Dr. Med. Oliver Ganslandt (Departments of Neurosurgery, Experimental Neuropsychiatry and Neurology, University of Erlangen-Nuremberg, Erlangen, Germany) and Prof. Rudolf Fahlbusch (Director of the Center for Endocrine Neurosurgery, International Institute for Neuroscience, Hannover, Germany) published most of the papers (51, 48 respectively).

Among the 93 publishing countries, the United States ranked first with 784 papers. American publications increased especially after 1999 (Figure 2). Most of these articles were published in 2019 (72 articles). Germany ranked 2nd with 683 articles (Table 2).

The University of Toronto (Canada) has published most of the papers on neuronavigation. The other top ten institutions publishing on neuronavigation were located in developed countries. Institutions from China, European countries (Germany, Austria, Norway), Canada, and the United States were among the top 10 list of top publishers of neuronavigation-related papers (Table 3). As can be seen in Figure 3, the blue color indicates the University of Erlangen-Nuremberg in Germany, where publications gained momentum towards the end of the 2000s. However, the University of Toronto in Canada, shown in pink, made a major breakthrough in 2017 (Figure 3).

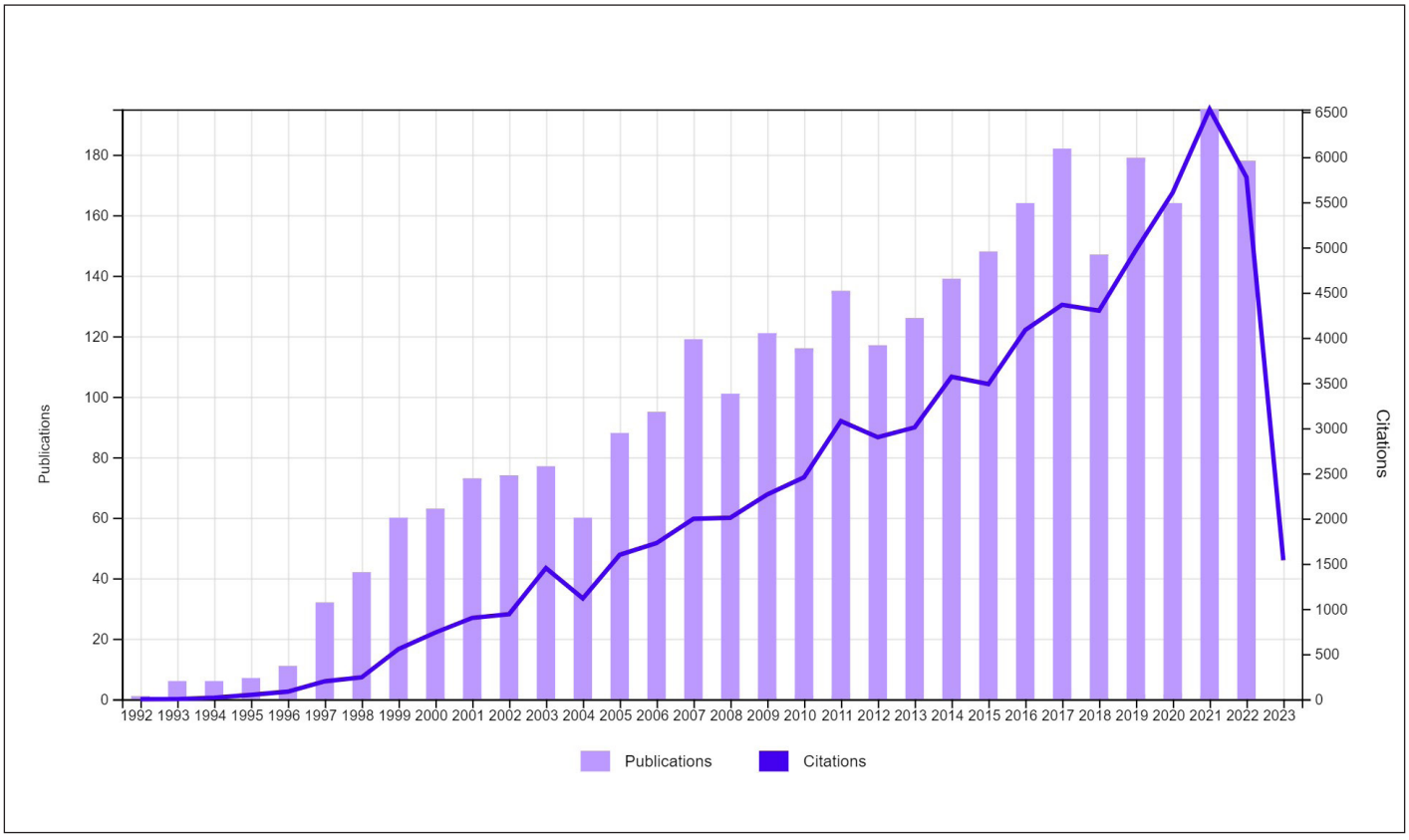


Figure 1. Publications and Citatons Over Time

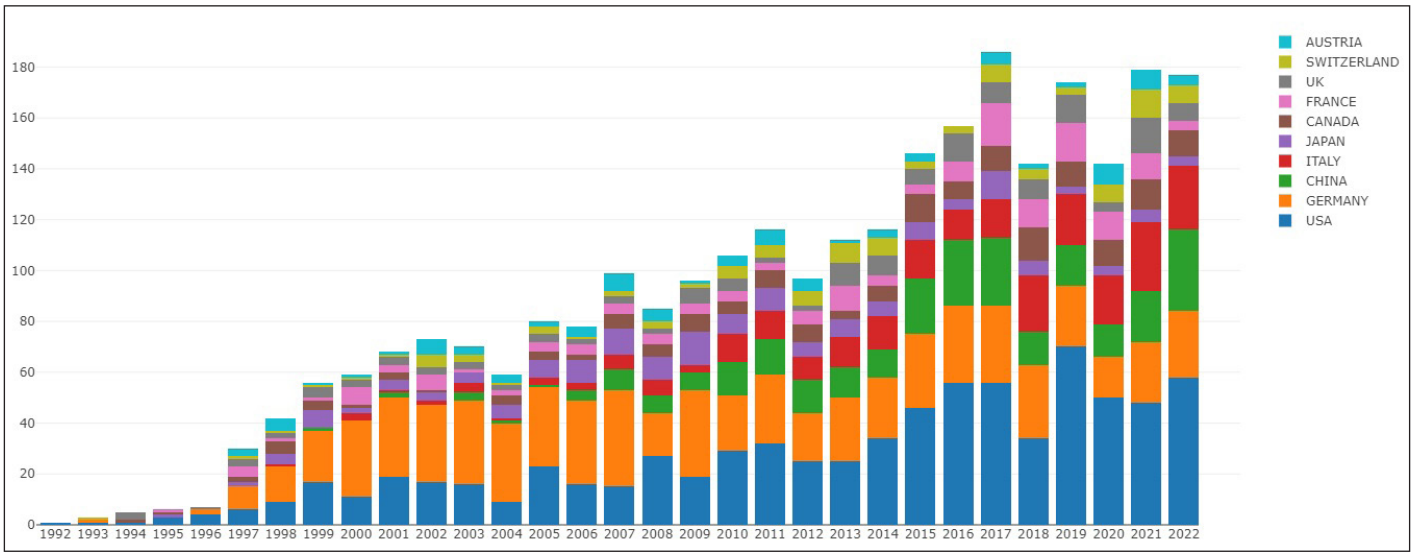
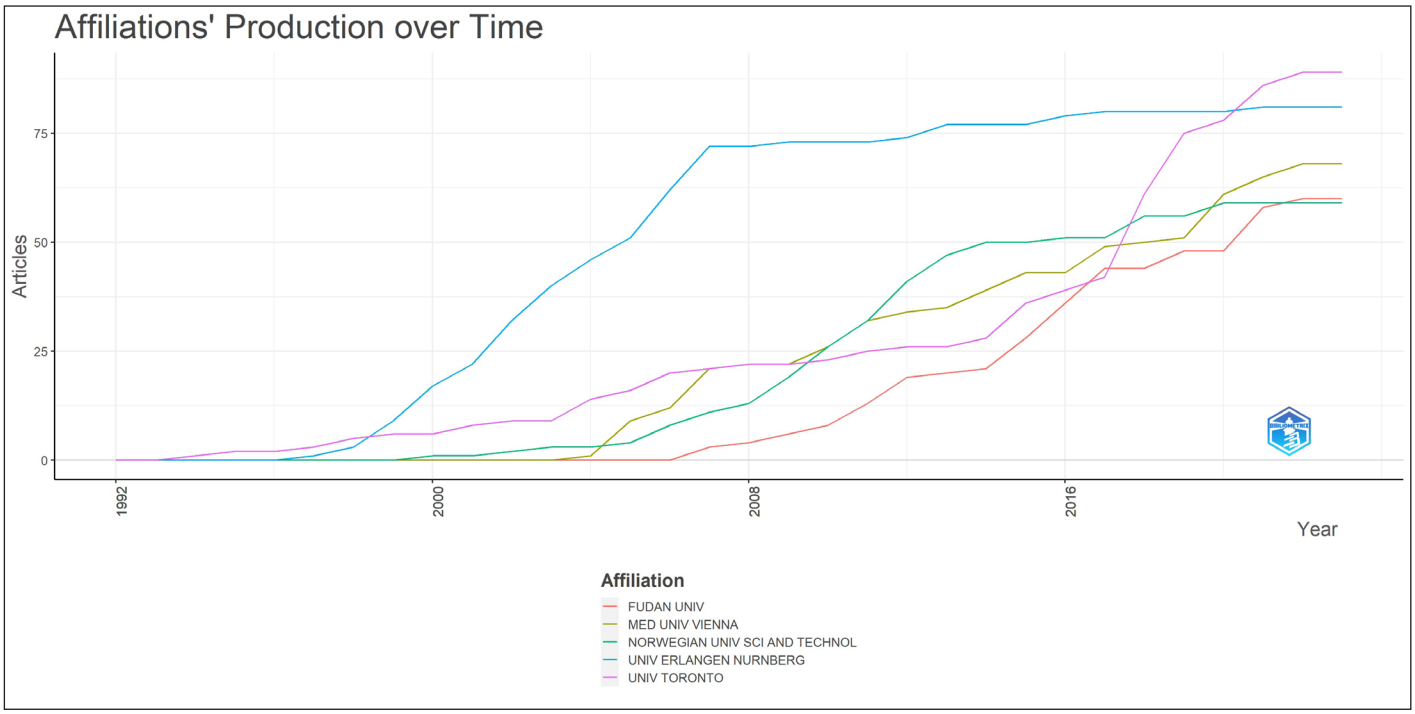


Figure 2. The number of publications of the mostly publishing countries over years



Figer 3. Affiliations' Production over Time

Table 2. Mostly publishing countries and citation analysis of these countries

Country	Total number of articles	Total citations	Average citations	H index
The United States	784	21287	27.15	73
Germany	683	21351	31.26	71
Italy	245	4748	19.38	34
China	240	2801	11.67	26
Japan	163	2870	22.92	34

Table 3. Most Relevant Affiliations

Ranking	Affiliation/Country	Number of articles
1	The University of Toronto, Canada	89
2	University of Erlangen-Nuremberg, Germany	81
3	The Medical University of Vienna, Austria	68
4	Fudan University, China	60
5	Norwegian University of Science and Technology, Norway	59
6	Hravard UNiversity, the United States	53
7	McGill University, Canada	53
8	The University of California, San Francisco, the United States	48
9	The University of Freiburg, Germany	48
10	Barrow Neurological Institute, the United States	46

Publishing Journals

Publications on neuronavigation were published in 575 different journals and Neurosurgery (214 articles), World Neurosurgery (200 articles), Journal of Neurosurgery (177 articles), Acta Neurochirurgica (156 articles) ranked first in the ranking of journals that published the most publications. The summary of the journals that published the most publications on neuronavigation is given in Table 4.

Citations over time and highly cited articles

The first article [23] was cited 26 times. The total number of citations was 71548 (57950 excluding self-citations), the average number of citations per article was 23.64 and the h-index was 108. In 2021, the most productive year, there were 195 articles and 6528 citations. After 2004, there was an acceleration in the number of publications and citations (Figure 1).

The most cited paper was published in 2003 by Herwig et al [25] and cited 661 times. Black et al [26] also published the second most cited paper on neuronavigation. This paper was published in 1997 and received 607 citations. The 20 most cited papers on neuronavigation are given in Table 1.

The United States published most of the articles, but Germany had higher citation counts (21287 vs. 21351 respectively) and also average citation counts per article (27.15 vs. 31.26). However, American publications had the highest H-index. A summary of the citation parameters of the top publishing countries is given in Table 2.

Keyword Analysis and Trend Topics

A total of 4541 keywords and 3602 keywords plus were used in these publications. Statistical results of keyword analysis were analyzed and summarized by the Literature Metrology Online Analysis Platform (Figure 4a and Figure 4b) and Bibliosiny [22] (Figure 4c). Also statistical results of trend topic analysis were analyzed and summarized by Bibliosiny [22] (Figure 5 and Table 5). Frequently used keywords can test whether a research area is hot in a given period and can highlight emerging topics. Figure 4a and Figure 4b illustrate the distribution of keywords and plus keywords by year. According to (Figure. 4c), neuronavigation—the same as the research topic—is the word with the highest frequency. Based on (Figure 4c), the second biggest word is surgery, also neuronavigation is a surgical method in neurosurgery. MRI, CT, and USG are diagnostic methods used in neuronavigation; brain tumors and sup-topic glioblastoma multiforme are among the main keywords.

Neuronavigation (747 occurrences), frameless stereotaxy (214 occurrences), image-guided surgery (119 occurrences), Glioma (115 occurrences), and Neurosurgery (86 occurrences), were among the top trend topics (Table 5).

Table 1.

First author	Title	Source Title	Publication Year	DOI	Total Citations
Herwig, et al	Using the International 10-20 EEG System for Positioning of Transcranial Magnetic Stimulation	BRAIN TOPOGRAPHY	2003	10.1023/B:BRAT.0000006333.93597.9d	661
Black, et al	Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications	NEUROSURGERY	1997	10.1097/00006123-199710000-00013	607
Paus, et al	Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex	JOURNAL OF NEUROSCIENCE	1997	10.1523/JNEUROSCI.17-09-03178.1997	568
Nimsky, et al	Quantification of, visualization of, and compensation for brain shift using intraoperative magnetic resonance imaging	NEUROSURGERY	2000	10.1097/00006123-200011000-00008	408
Jakola, et al	Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	2012	10.1001/jama.2012.12807	407
Hopf, et al	Endoscopic third ventriculostomy: outcome analysis of 100 consecutive procedures	NEUROSURGERY	1999	10.1097/00006123-199904000-00062	381
Nabavi, et al	Serial intraoperative magnetic resonance imaging of brain shift	NEUROSURGERY	2001	10.1097/00006123-200104000-00019	360
Cardinale, et al	Stereoelectroencephalography: surgical methodology, safety, and stereotactic application accuracy in 500 procedures	NEUROSURGERY	2013	10.1227/NEU.0b013e31827d1161	356
Burgel, et al	White matter fiber tracts of the human brain: three-dimensional mapping at microscopic resolution, topography and intersubject variability	NEUROIMAGE	2006	10.1016/j.neuroimage.2005.08.040	319
Nimsky, et al	Preoperative and intraoperative diffusion tensor imaging-based fiber tracking in glioma surgery	NEUROSURGERY	2005	10.1227/01.NEU.0000144842.18771.30	305
GOLFINOS, et al	Clinical use of a frameless stereotactic arm: results of 325 cases	JOURNAL OF NEUROSURGERY	1995	10.3171/jns.1995.83.2.0197	301
Hu, et al	Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements	AMERICAN JOURNAL OF NEURORADIOLOGY	2009	10.3174/ajnr.A1377	280
Steinmeier,et al	Intraoperative magnetic resonance imaging with the magnetom open scanner: concepts, neurosurgical indications, and procedures: a preliminary report	NEUROSURGERY	1998	10.1097/00006123-199810000-00005	270
Herwig, et al	Transcranial magnetic stimulation in therapy studies: examination of the reliability of “standard” coil positioning by neuronavigation	BIOLOGICAL PSYCHIATRY	2001	10.1016/S0006-3223(01)01153-2	266
Sack, et al	Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods	JOURNAL OF COGNITIVE NEUROSCIENCE	2009	10.1162/jocn.2009.21126	261
Dorward, et al	Postimaging brain distortion: magnitude, correlates, and impact on neuronavigation	JOURNAL OF NEUROSURGERY	1998	10.3171/jns.1998.88.4.0656	255
Dickman, et al	Posterior C1-C2 transarticular screw fixation for atlantoaxial arthrodesis	NEUROSURGERY	1998	10.1097/00006123-199808000-00056	243
Tronnier, et al	Intraoperative diagnostic and interventional magnetic resonance imaging in neurosurgery	NEUROSURGERY	1997	10.1097/00006123-199705000-00001	239
Schroeder, et al	Complications of endoscopic third ventriculostomy	JOURNAL OF NEUROSURGERY	2002	10.3171/jns.2002.96.6.1032	232
Wu, et al	Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: a prospective, controlled study in patients with gliomas involving pyramidal tracts	NEUROSURGERY	2007	10.1227/01.neu.0000303189.80049.ab	231

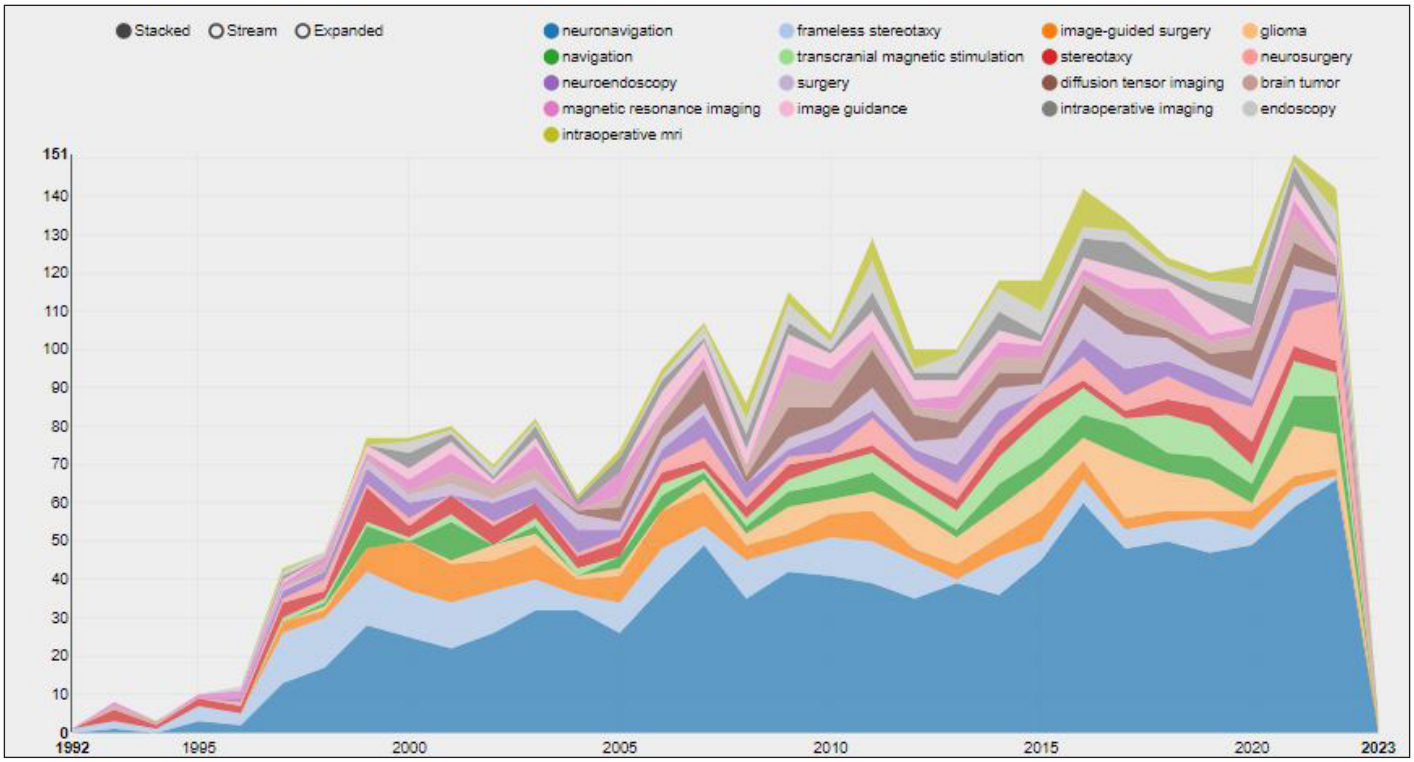


Figure 4a. Keywords by years

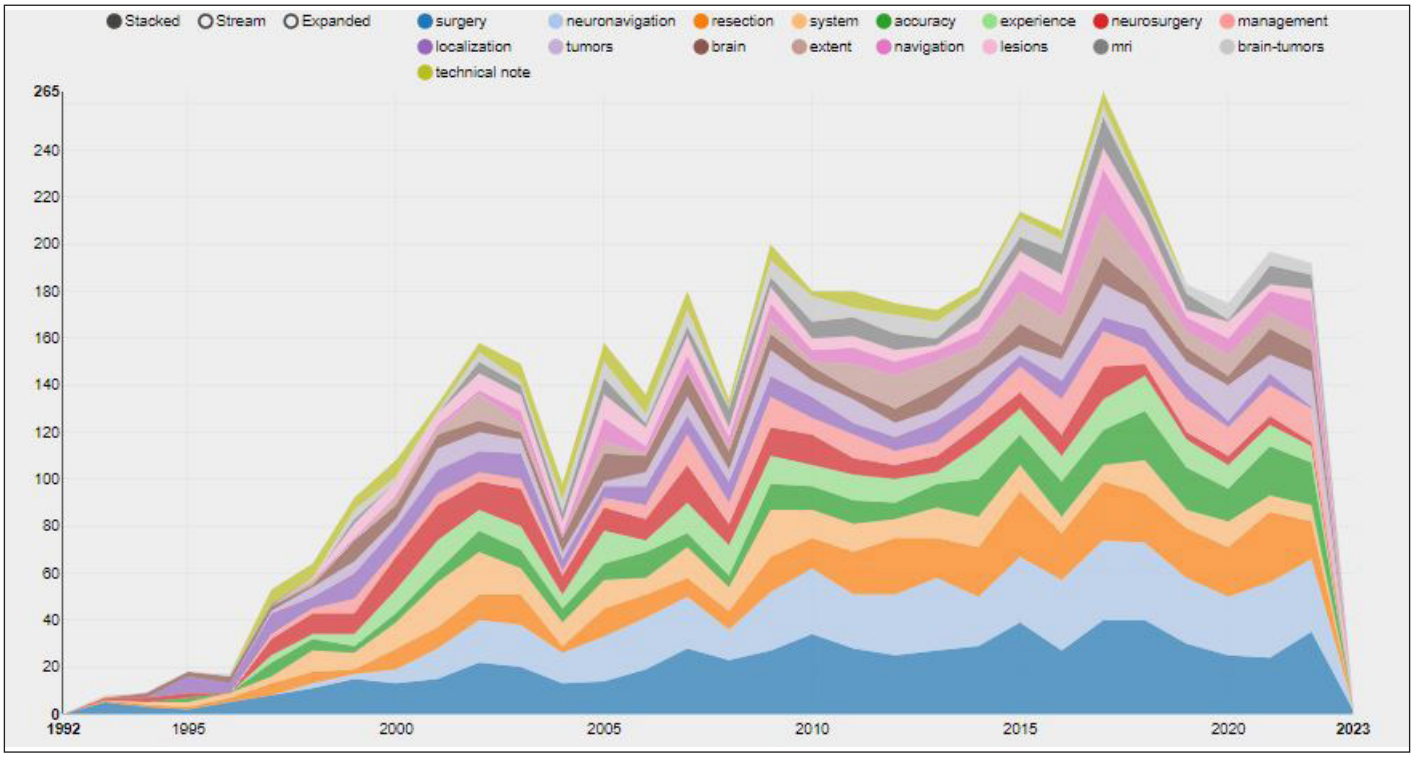


Figure 4b. Expand keywords by years

Figure 4c. Wordcloud

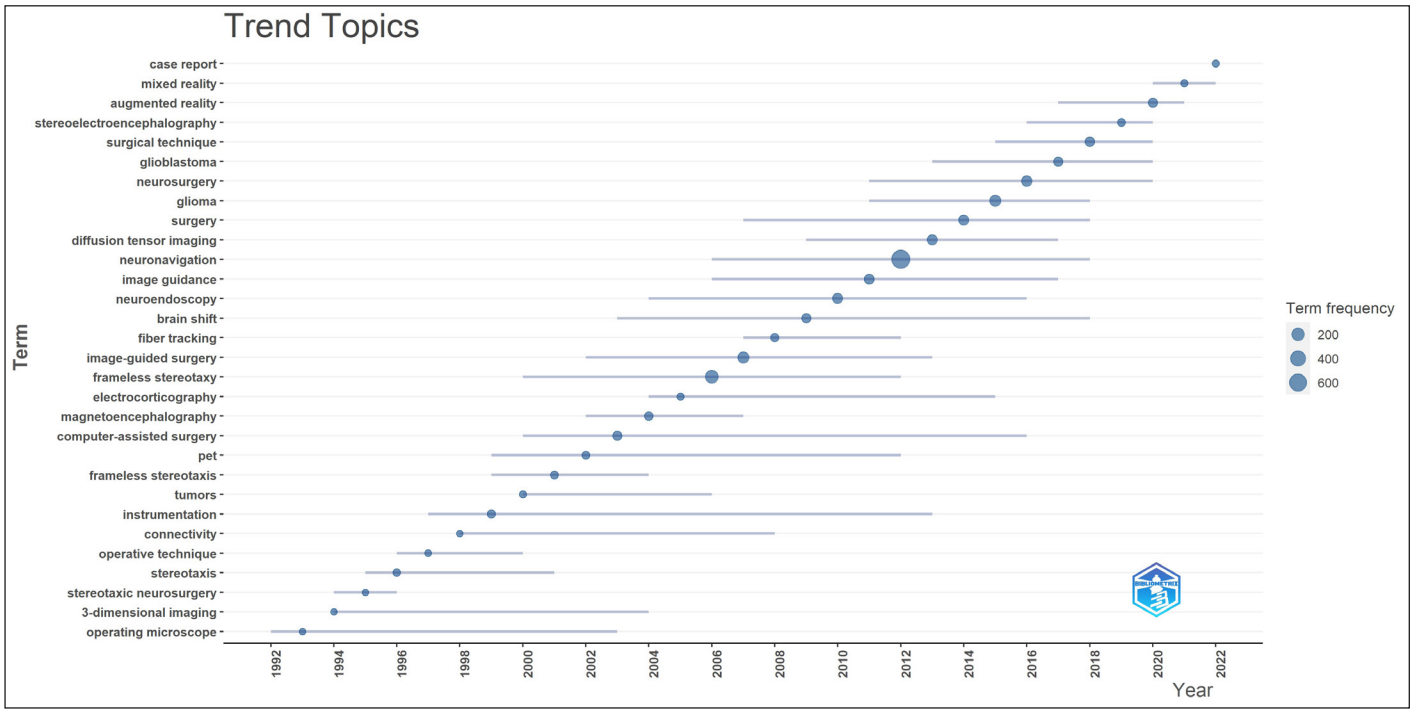


Figure 5. Trend topics

Table 4. Top publishing journals

Publication Titles	Article Count	%
Neurosurgery	214	7.072
World Neurosurgery	200	6.609
Journal Of Neurosurgery	177	5.849
Acta Neurochırurgıca	156	5.155
Mınımally Invasıve Neurosurgery	104	3.437
Operatıve Neurosurgery	84	2.776
Stereotactıc And Functıonal Neurosurgery	76	2.512
Chılds Nervous System	68	2.247
Clınıcal Neurology And Neurosurgery	57	1.884
Journal Of Clınıcal Neuroscıence	52	1.718
Neurosurgıcal Revıew	52	1.718
Neurosurgıcal Focus	48	1.586
Brıtısh Journal Of Neurosurgery	41	1.355

Journal Of Neurosurgery Pedıatrıcs	39	1.289
Internatıonal Journal Of Computer Assısted Radıology And Surgery	35	1.157
Neurologıa Medıco Chırurgıca	31	1.024
Neuroımage	30	0.991
Journal Of Neurologıcal Surgery Part A Central European Neurosurgery	29	0.958
Neurochırurgıe	29	0.958
Surgıcal Neurology	28	0.925
Turkısh Neurosurgery	25	0.826
Neurologıcal Research	24	0.793
Braın Stımulatıon	21	0.694
Neurosurgery Clınıcs Of North Amerıca	21	0.694
Journal Of Neuro Oncology	20	0.661

*Showing 25 out of 575 journals

Table 5. Trend topics

Item	Freq	year_q1	year_med	year_q3
Neuronavigation	747	2006	2012	2018
Frameless Stereotaxy	214	2000	2006	2012
Image-Guided Surgery	119	2002	2007	2013
Glioma	115	2011	2015	2018
Neurosurgery	86	2011	2016	2020
Diffusion Tensor İmaging	81	2009	2013	2017
Surgery	78	2007	2014	2018
Neuroendoscopy	74	2004	2010	2016
Image Guidance	65	2006	2011	2017
Surgical Technique	50	2015	2018	2020
Brain Shift	47	2003	2009	2018
Glioblastoma	46	2013	2017	2020
Computer-Assisted Surgery	45	2000	2003	2016
Augmented Reality	42	2017	2020	2021
Magnetoencephalography	25	2002	2004	2007
Fiber Tracking	20	2007	2008	2012
Instrumentation	17	1997	1999	2013
Frameless Stereotaxis	16	1999	2001	2004
Pet	14	1999	2002	2012
Stereoelectroencephalography	13	2016	2019	2020
Stereotaxis	9	1995	1996	2001
Tumors	7	2000	2000	2006
Electrocorticography	6	2004	2005	2015
Mixed Reality	6	2020	2021	2022
Case Report	6	2022	2022	2022
Operative Technique	4	1996	1997	2000
Operating Microscope	3	1992	1993	2003
3-Dimensional İmaging	3	1994	1994	2004
Stereotaxic Neurosurgery	3	1994	1995	1996
Connectivity	3	1998	1998	2008

* freq: number of occurrance, Year q1: first occurance year, year_q3: last year of occurance, year_med: most frequently occured year

DISCUSSION

Although this topic is of great interest in the field of neurosurgery, no published bibliometric study has been published on how the scientific literature has evolved. There was one similar study using machine learning methods for topic analysis on neuronavigation research [30]. In this study [30] PubMed database was used to obtain data. In the current study, the Web of Science database was used to retrieve the study's data. The Web of Science database is a bibliometric analysis database frequently used in similar studies [9,11,1531-34]. In this study, general information about the bibliometric parameters such as the most prolific authors/organizations/countries, most published journals, number of citations, H-indexes, etc. were analyzed. And also keywords and trending topics were also analyzed and visualized using detailed visualization programs.

There were 3896 articles, according to Watanabe's study [27]. The quantity of neuronavigation publications increased by 80% between 1999–2009 and 2010–2020. There was a 0.3% decrease between 2009-2014 and 2015-2020. According to the current study, there was an acceleration in the number of publications and citations after 2004. This difference may be due to the fact that Pubmed and Web of Science databases index different journals.

The first scientific data on neuronavigation technologies were first published in the United States [4], and in the following years, great progress was made in Japan [28], the United States [29] and Germany [30]. Although neuronavigation was first actively implemented in four neurosurgical facilities in Romania in 2003 [3], according to the results of the present study, Romania was not included in the ranking of both the countries with the most publications or the countries with the most publications. Among 93 publishing countries, the United States took first place with 784 articles. American publications increased especially after 1999. Germany ranked 2nd with 683 articles. Institutions from China, European countries (Germany, Austria, Norway), Canada, and the United States were among the top 10 lists of top publishers of these articles. Watanabe's study [27] does not address the issue of broadcasting institutions or countries. Also in the current study, the top cited 20 articles were summarized.

Since analyzing in which journals the most publications on a topic are published can guide researchers on that topic, the journals that publish the most publications were also examined in this study. Neurosurgery (214 articles), World Neurosurgery (200 articles), Journal of Neurosurgery (177 articles), and Acta Neurochirurgica (156 articles) ranked first in the ranking of journals that published the most publications. These journals are also among the most prestigious journals in the field of neurosurgery.

In bibliometric research, a researcher must choose a number of keywords to serve as a representation of the primary study themes in the area if they hope to learn more about the specifics of the major research issues of a field and their micro-level relationships. Prior research had a tendency to choose keywords based on network-based measurements or frequency, both of which have been shown to be substantially connected with keyword frequency [35]. Studies that use keyword frequency analysis for hotspot detection and trend analysis are relevant [36]. Also, the bibliometrics idea states that keywords reveal hotspots and trends in a research area. As keywords indicate the subject matter of an article or an author, they also offered a typical overview of research trends that applied to the publication [37]. A common strategy for revealing the knowledge structure of study areas is to use publication keywords. The choice of which keywords should be preserved as analysis objects once a large number of keywords are acquired from domain publications is a significant but under-addressed subject [36]. Therefore, trend topic and keyword analysis were given priority in this study. According to Watanabe's study [27], publications within the top 10 topics were further analyzed by obtaining citation counts, main MeSH terms, and MeSH subheadings. Google Scholar was used to calculate the number of citations. The number of publications and citations in the current study were calculated using data and graphs from the Web of Science database. According to Watanabe's research [27], the most commonly assigned themes were "brain", "brain neoplasms", "MRI", and "3D imaging" and neuronavigation research is increasingly focusing on clinical evaluation of existing neuronavigation tools rather than the development of new systems. Neuronavigation research on standards, education, adverse effects, and economics is limited. This study [27] identified distinct themes in neuronavigation research and quantified their representation and growth in the academic literature. In the current study, neuronavigation—the same as the research topic—is the word with the highest frequency. The second biggest word is surgery, also neuronavigation is a surgical method in neurosurgery. MRI, CT, and USG are diagnostic methods used in neuronavigation; brain tumors and sup-topic glioblastoma multiforme are among the main keywords. Neuronavigation (747 occurrences),

frameless stereotaxy (214 occurrences), image-guided surgery (119 occurrences), Glioma (115 occurrences), and Neurosurgery (86 occurrences) were among the top trend topics.

Limitations

This study included a single database data. The time range was limited to 1990-31 December 2022. The year 2023 was excluded as the year was not yet complete and database updates were still ongoing. For these reasons, it may not reflect all the literature.

CONCLUSION

The results of this study show that neuronavigation research in neurosurgery will continue to be a topic open to development with today's advancing technology. As a result, this study can reveal the trends and characteristics of neuronavigation studies and provide researchers with ideas for future research. According to both the number of citations and publications the leading countries were the United States and Germany. Apart from the United States and Germany, neuronavigation publications are increasing and are likely to continue to increase in countries such as China, European countries (Germany, Austria, Norway), and Canada.

Informed Consent: None.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Original Research

Bibliometric and Visual Analysis of Palliative Nutrition Research Based on Web of Science

Sevil Alkan[1], Murat Emre Tokur[2]

[1] Infectious Disease Department, Canakkale Onsekiz Mart University Faculty of Medicine, Turkey
[2] Department of Chest Diseases, Department of Intensive Care, Ege University Faculty of Medicine, İzmir, Turkey

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Correspondence
Sevil Alkan, MD
Address: Canakkale Onsekiz Mart University Faculty of Medicine, Infectious Disease Department, Çanakkale / Turkey
E-mail: sevil3910@gmail.com

ABSTRACT

Objective: Nutritional therapy has been shown to reduce the mortality rates of critically ill individuals. In recent years, there has been a significant increase in scholarly curiosity about the growing use of palliative nutrition. In order to determine the global research output on palliative nutrition, this bibliometric analysis was conducted to assess the current status of research trends and research directions.

Methods: The bibliometric data of the study was obtained from the online database Web of Science and analyzed and visualized with Excel, the Bibliometrix R package (version 4.1.2), and the bibliometric online application (https://bibliometric.com/app) tools.

Results: A total of 1067 publications were included in this study. The majority of publications (398,37.30%) and citations (n: 9252) in this discipline have come from the United States. The most frequent publication type detected was article (n: 794). Publications published in 398 different sources (journals/books etc.). The international co-authorship rate was 11.62%. In the last 20 years, the annual number of publications has drastically expanded. The highest number of publications was published in 2020 and 2021 (n: 67, and n: 64 respectively). Australia, France, Canada, Japan, and China stand out as the countries with the highest number of publications in recent years. The terms 'end, care, hydration, nutrition, life, decision-making, artificial nutrition, and palliative care' were the most preferred keywords.

Conclusion: Finally, given the number of palliative care patients globally is expected to rise, it is critical to do ongoing research on appropriate nutritional therapy for these patients. As our study shows study gaps and study trends, it can provide insight for future work in this field.

Keywords: bibliometric analysis; critical care; intensive care unit; enteral nutrition; parenteral nutrition; palliative; visual analysis.

INTRODUCTION

The World Health Organization (WHO) definition of palliative care is 'comprehensive care provided to patients with medical conditions that do not improve with treatment'. By addressing issues such as pain management, biopsychosocial difficulties, and spiritual requirements, palliative care aims to enhance the life quality for patients and those closest to them [1]. There is a holistic approach in palliative care which includes dietary counselling, rapid nutrition support, and management of feeding-related problems. These aspects should be tailored to the patient's stage in life and taken into account when making decisions about diet and nutrition. As the population ages and the number of individuals with various life-limiting diseases expands, nutrition management for these patients is becoming harder to manage [2].

Nutritional therapy is an important part of the care of critically ill patients. However, the optimal nutritional strategy is still debated and often causes a challenge in clinical practice. Guidelines from various nations have differing, such as the German Society for Nutritional Medicine (DGEM) [3], the European Society for Enteral and Parenteral Nutrition (ESPEN) [4], the American Society for Enteral and Parenteral Nutrition (ASPEN) [5] and other associations [6]. Furthermore, the wide range of underlying diseases of these patients ought to be considered as a basis for personalized choices made for each patient [7].

More research has revealed that feeding methods can reduce metabolic stress, avoid oxidative cellular damage, and modulate immunological responses [8]. Therefore, over the last 40 years, nutritional research for seriously ill patients has shifted from observational studies to large randomized controlled trials with long-term follow-up studies [9]. Published guidelines on nutrition therapy for critically ill patients have been updated in accordance with the new ESPEN Standard Operating Procedures. This update details risk groups, assessment of nutritional status, how to calculate the amount of energy required, the pathway to follow, and how to adapt to various clinical circumstances. It also recommends best practices for determining the amount and type of carbohydrate, fat, and protein for planning the initiation and continuation of nutritional support. There is a special focus on omega-3 fatty acids and glutamate. This guideline details specific conditions common in intensive care, such as dysphagic individuals, frail patients, multi-trauma patients, abdominal surgery, sepsis, etc., to help health professionals choose the best evidence-based treatment [4].

Main Points;

- This study is the first bibliometric study on palliative nutrition.
- The United States (n = 400), the United Kingdom (n = 101), Italy (n = 68), the Netherlands (n = 61), and Canada (n = 54) were among the countries with most publications.
- The number of publications from developing countries was limited.
- Germany, the Netherlands, the United States of America, the United Kingdom, and Belgium were the countries with the most multi-country publications.
- The terms of advance care planning, end-of-life, decision-making, and tube feeding were trending topics.

The topic of our research lies on the outer boundaries of three major research areas: geriatrics, intensive care medicine, and nutrition and dietetics. As a result, it is difficult to define the precise boundaries of the study areas and it is difficult to have a solid picture of the changes and activities related to the topic. However, a thorough grasp of research discoveries and specialist emphasis would be advantageous for researchers, physicians, and patients participating in this field. In this investigation, we conducted a bibliometric study to address the aforementioned issues. We aimed to reveal the existing status of research topics and dynamics in the field, as well as the most important topic advances in research focus. Our findings can support the expansion of the scope of palliative nutrition research.

MATERIALS AND METHODS

A public data repository of an electronic database was employed in the current investigation, which was exempt from ethical approval. The Web of Science electronic database's core collection was selected to search and retrieve the publications.

The search terms were as follows: TS=(Nutritional Sciences OR Nutrition Assessment OR Nutrition Therapy OR Nutrition Policy OR nutrition* OR diet OR feeding OR dietary OR complementary feeding OR Feeding Methods OR nutritional status OR under nutrition OR food OR food and beverages OR micronutrient* OR vitamin* OR macronutrient* OR carbohydrate* OR caloric intake OR energy intake) English was chosen as the language of publications.

The time span was selected 1970, 1 January, and 31 April 2023. The first search showed 379,595 results with selected keywords. Since we aimed to search for publications related to palliative care, we narrowed the search with the words 'palliative care' and 'intensive care unit' in the Citation Topics Micro and Citation Topics Macro sections of the search engine. Since the subject of the study is extremely broad and multidisciplinary publications may cause bias, limitations were made with the help of Citation Topics Micro and Citation Topics Macro subheadings. In this field, we focused only on nutrition in palliative care. We reached 1067 results according to the search methodology.

For analysis, the exported data was stored as plain text, tab limited format, and file exported from Excel as "full records and cited references." The files downloaded to the computer by two researchers were checked. As a result of 99% consensus, the files to be analyzed were selected. Data from publications with

inconsistency were excluded.

Visualization and analysis of data

It was aimed to analyze many bibliometric data such as; the general characteristics of the publications, the journals with the most publications, the institutions/universities with the most publications, and the distribution of the number of publications of these institutions over the years, the most cited and publishing countries and the H indexes of these countries, the most used keywords, the density of keywords over the years, etc.

For this purpose, we used Excel, the Bibliometrix R package (version 4.1.2) [10] and the bibliometric online application (https://bibliometric.com/app) for analysis, to create tables and figures.

RESULTS

According to our search criteria, 1067 documents were included in this bibliometric evaluation. The majority of publications (n: 398, 37.30%) and citations (n: 9252) in this discipline have come from the United States, which has contributed the most. The most frequent publication type detected was an article (n: 794), followed by a review (n: 113), editorial content (n: 61), and a letter (n: 34). Publications related to our study topic were published in 398 different sources (journals/books etc.). 244 publications were published by a single author. The international co-authorship rate was 11.62%. Summary information about the publications included is given in Table 1. There were very few publications between 1983 and 1990. In the last 20 years, the annual number of publications has drastically expanded. The annual growth rate of these publications was 5.34%. The highest number of publications was published in 2020 and 2021 (n: 67, and n: 64 respectively). The volume of publications varied between 2003 and 2022, although they grew overall. In 2023, the number of publications seems to have decreased, but this graphical data may be misleading as this year has not yet been completed. The annual scientific output is displayed by years in Figure 1 and annual citation numbers are displayed by years in Figure 2. These 1067 publications originated from 59 countries. According to the countries that published the most articles throughout the span of time, the number of publications has been shown in Figure 3a. Figure 3a was created with the bibliometric online application (https://bibliometric.com/app). Figure 3a shows that Australian and Chinese publications have been on an increasing trend since 2000. American researchers were the first authors to publish on this topic. American publications have been available since the early 1980s. Canadian publications started in the first half of the 1990s, and Canadian publications have increased tremendously, especially in the last 20 years. Researchers from Japan and France have also published an increasing number of publications since the 2000s. Australia, France, Canada, Japan, and China stand out as the countries with the highest number of publications in recent years. Figure 3b visualizes the number of publications by country of the corresponding authors. The red areas in Figure 3b show the numerical distribution of multi-country collaborative publications (MCP) and the green areas show the numerical distribution of single-country publications (SCP). Germany, the Netherlands, the United States of America, the United Kingdom, and Belgium were the countries with the most multi-country publications. In other words, they were the countries with international collaborations (Figure 3b).

Table 1. Main information

Description	Results
Maın Informatıon	
Timespan	1983-2023
Sources (Journals, Books, Etc)	398
Documents	1067
Annual Growth Rate %	5.34
Document Average Age	12.2
Average Citations Per Doc	19.62
References	21457
Document Contents	
Keywords Plus	1161
Author's Keywords	1363
Authors	3406
Authors Of Single-Authored Docs	214
Authors Collaboratıon	
Single-Authored Document	244
Co-Authors Per Document	4.21
International Co-Authorships %	11.62
Document Types	
Article	794
Article; Book Chapter	20
Article; Early Access	9
Article; Proceedings Paper	20
Correction	4
Editorial Material	61
Letter	34
Meeting Abstract	4
Note	3
Proceedings Paper	4
Reprint	1
Review	113

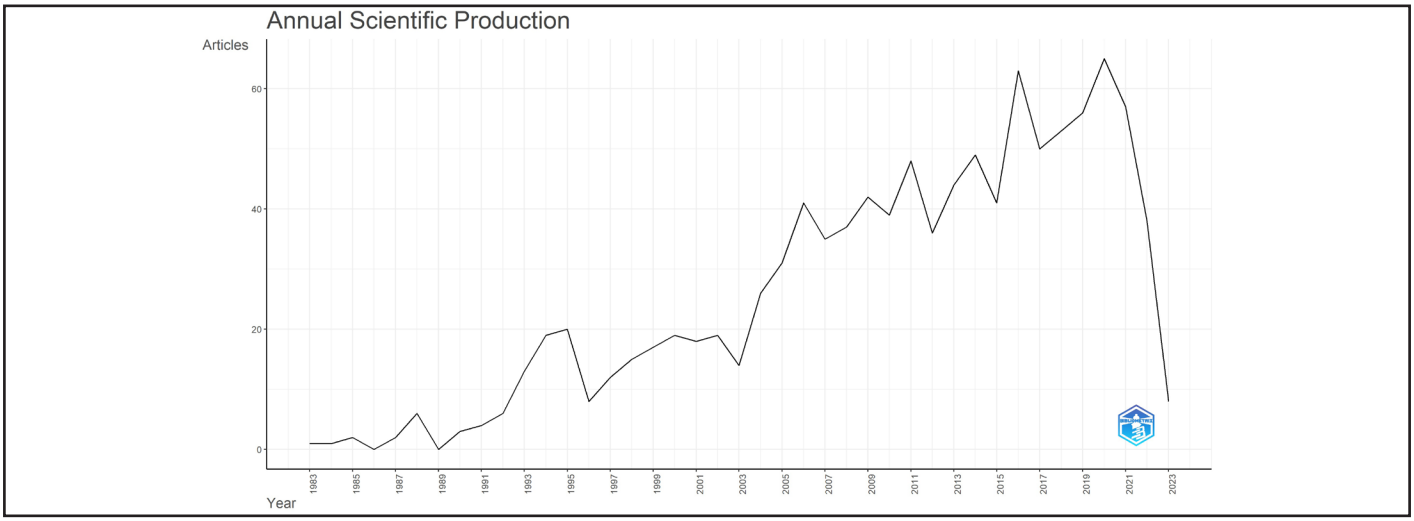

Figure 1. Annual Scientific Production

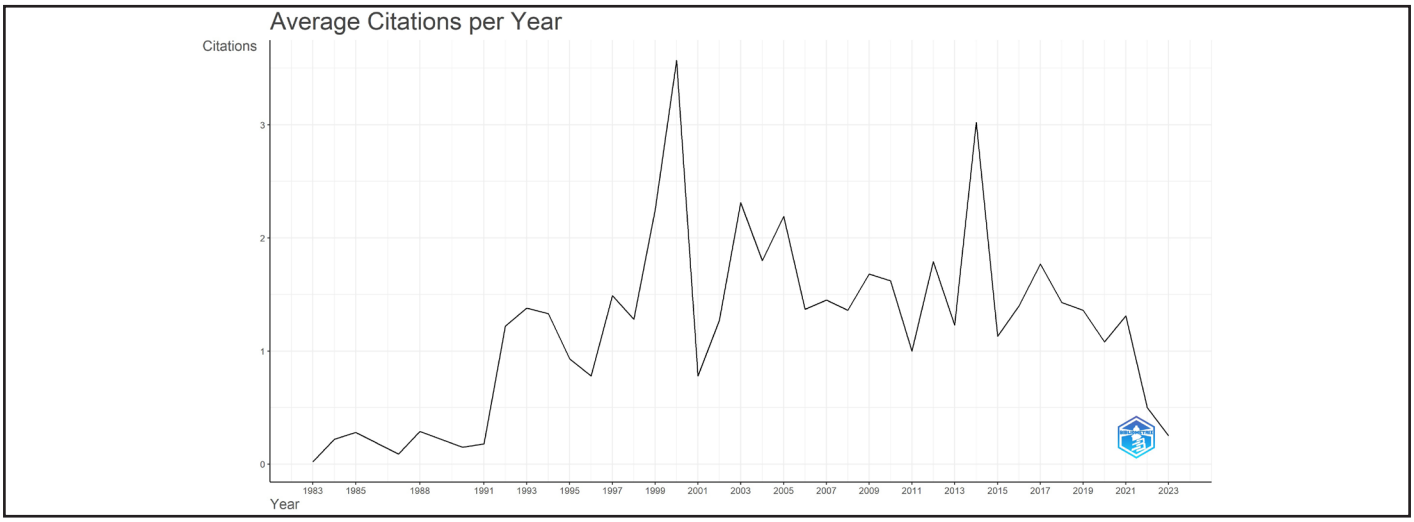

Figure 2. Average Citations Per Year

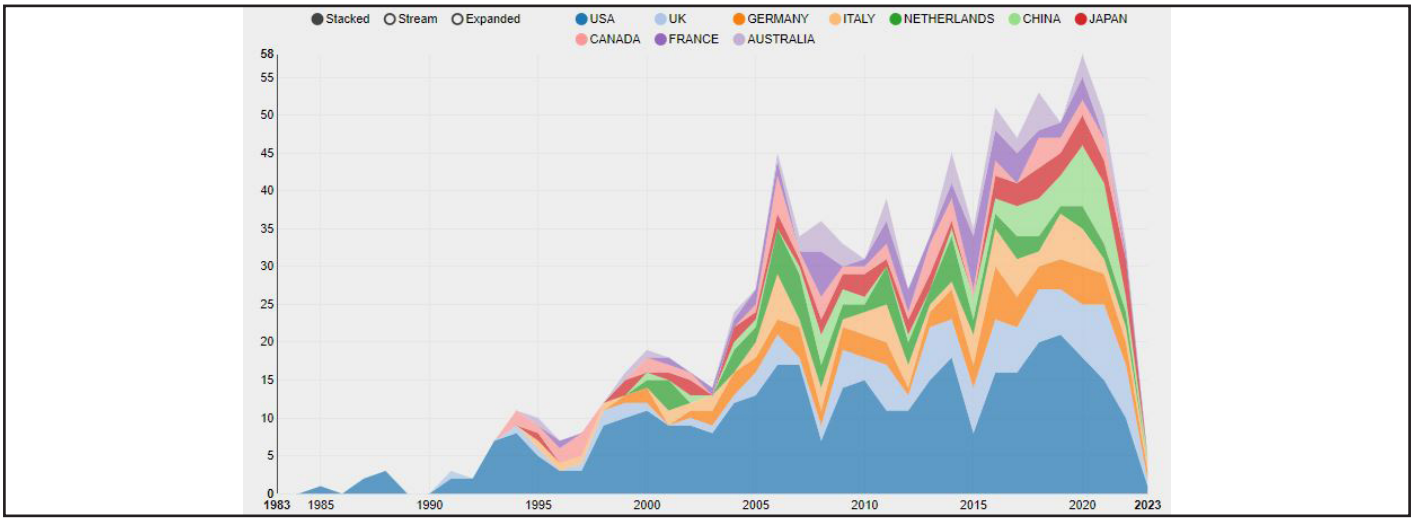

Figure 3 a. Changes in the number of articles by country over the years

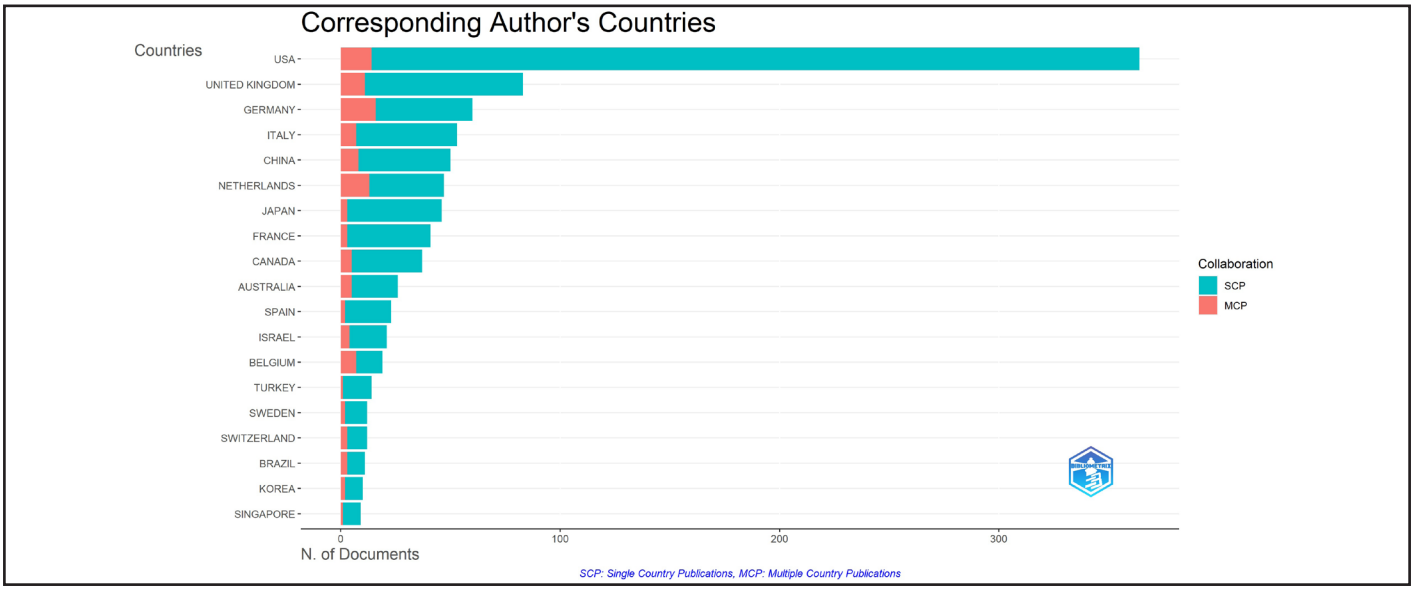

Figure 3 b. Corresponding Author's Countries

Journal of Pain and Symptom Management, Journal of the American Geriatrics Society, Journal of Medical Ethics, Journal of Palliative Medicine, and Journal of Palliative Medicine were the journals which included the most publications on palliative nutrition. Table 2 summarizes the journals with the highest number of publications on this topic. The Journal of the American Geriatrics Society, the Archives of Internal Medicine, and the Journal of Medical Ethics were the most cited journals. The H index, the total number of publications, and citations of the most influential journals are summarized in Table 3. Figure 4 shows that the top 5 journals with the highest number of publications all started publishing on nutrition in the 1990s, the first publications were published by the Journal of the American Geriatrics Society and there has been a dramatic increase in the number of publications in these journals since the early 2000s.

Table 4 shows the institutions/universities with more than 15 publications on palliative nutrition. According to Table 4, when we look at the countries of the institutions in this list, the majority of them were located in the United States. According to this table, the top 5 most productive institutions were the National Taiwan University (Taiwan), the Vrije Universiteit Amsterdam (the Netherlands), the University of Pennsylvania (the United States), the University of North Carolina (the United States), and Indiana University Bloomington (the United States). Figure 5 shows the production of the most productive institutions over time. The Vrije Universiteit Amsterdam was the first to publish publications on this topic. Publications from other institutions also started to appear in the early 1990s. The number of publications started to increase rapidly after 2006 (Figure 5).

The United States (n: 400), the United Kingdom (n: 101), Italy (n: 68), the Netherlands (n: 61), and Canada (n: 54) are among the countries with the highest number of publications on palliative nutrition. In Figure 2, the countries of the corresponding authors are analyzed, while Table 5 analyzes the countries of all authors (corresponding and co-authors). The data used in this table were downloaded from the Web of Science database and tabulated. As seen in Table 5, the countries with the highest total number of citations were the United States with 9252 citations, the Netherlands with 2005 citations, and England with 1616 citations. However, in the detailed analysis made with the Biblioshiny program, the Netherlands, where eight publications were published, was the country with the most publications that received citations (n: 50).

According to the analysis with the Biblioshiny program 'end, care, hydration, nutrition, life, decision-making, artificial nutrition, and palliative care' terms were the most preferred keywords among 1363 author keywords. Table 6 shows the occurrence rates of these keywords. Figure 6a visualizes the frequency of the most used keywords on nutrition. Figure 6b visualizes the most frequently preferred keywords by year. According to this, 'advance care planning, end-of-life, decision-making, and tube feeding' topics have been trending in recent years, and the topic of ethics has been trending especially since the early 1990s. Figure 6b was created with the bibliometric online application (https://bibliometric.com/app).

Table 2. Most relevant journals on nutrition studies

Journals	Number of Publications
Journal of Pain and Symptom Management	39
Journal of the American Geriatrics Society	37
Journal of Medical Ethics	31
Journal of Palliative Medicine	31
Palliative Medicine	28
Supportive Care in Cancer	25
American Journal uf Hospice & Palliative Medicine	23
Archives uf Internal Medicine	20
Medecine Palliative	17
Nutrition in Clinical Practice	17

Table 3. Journals' local impact on nutrition studies

Journals	H_index	Tc	Np
Journal of the American Geriatrics Society	20	1396	37
Archives of Internal Medicine	16	1434	20
Journal of Medical Ethics	16	569	31
Journal of Pain And Symptom Management	16	949	39
Supportive Care in Cancer	14	631	25
Journal of Palliative Medicine	13	825	31
Palliative Medicine	13	1122	28
Bmc Palliative Care	9	188	16
Pediatrics	9	475	10
Jama-Journal of the American Medical Association	8	1575	12

*TC: total citations, NP: number of publications

Table 4. The institutions/universities with more than 15 publications on nutrition

Affiliation	Number of publications
National Taiwan University/Taiwan	27
The Vrije Universiteit Amsterdam/Holland	27
University of Pennsylvania/ The United States	26
The University of North Carolina/ The United States	24
Indiana University Bloomington/ The United States	21
The University of Toronto/ Canada	21
University of Washington/ The United States	19
Harvard University/ The United States	18
Ghent University/ Belgium/Taiwan	18
National Taiwan University Hospital	17
Seirei Mikatahara General Hospital/Japan	17
The University of Chicago/ The United States	17
University of Lausanne/Switzerland	17
The University of Tokyo/Japan	16

Table 5. Most cited countries

Country	Number of Publications	Total Citations	Average Article Citations
The Usa	400	9252*	25.40
Netherlands	61	2005	42.70
England	101	1616	19.50
Canada	54	1067	28.80
Italy	68	856	16.20
Japan	51	731	15.90
China	15	608	12.20
Israel	24	588	28.00
Germany	70	534	8.90
Australia	41	419	16.10
Belgium	30	388	20.40
France	46	279	6.80
Spain	33	174	7.60
Austria	12	153	19.10
Swıtzerland	29	152	12.70
Denmark	8	150	50.00*
Korea	12	145	14.50
Sweden	22	115	9.60

*Shows the highest numbers

Table 6. Most frequent words

Words	Occurrences
End	223
Care	212
Hydration	167
Nutrition	159
Life	138
Decision-Making	126
Artificial Nutrition	114
Palliative Care	110
Death	89
Percutaneous Endoscopic Gastrostomy	74
Attitudes	73
Nursing-Home Residents	73
Survival	70
Physicians	61
Support	56
Cancer	51
Advanced Dementia	50
Of-Life Care	50
Patient	49
Decisions	48
Quality	47
Advance Directives	45
Cancer-Patients	44
Outcomes	44
Preferences	44

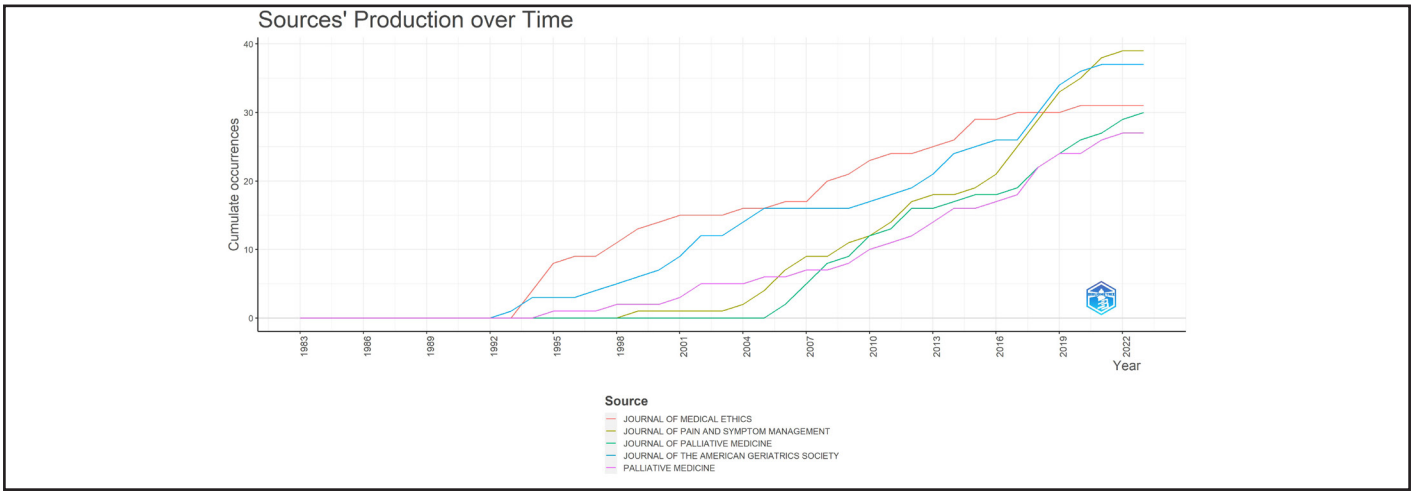

Figure 4. Top Journals' Production over Time

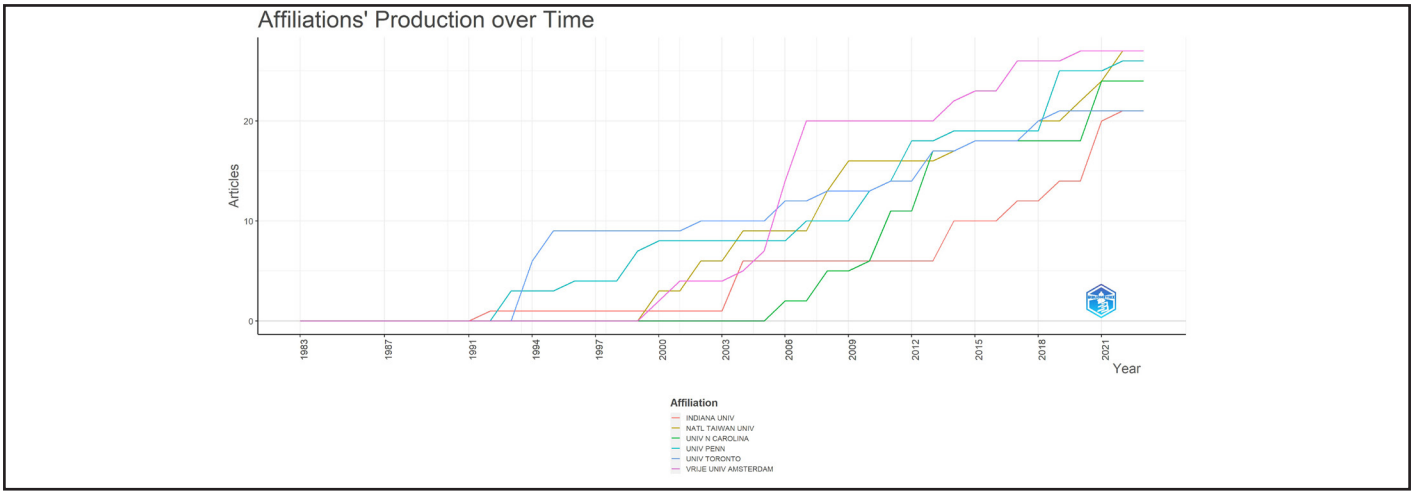

Figure 5. Affiliations' Production over Time

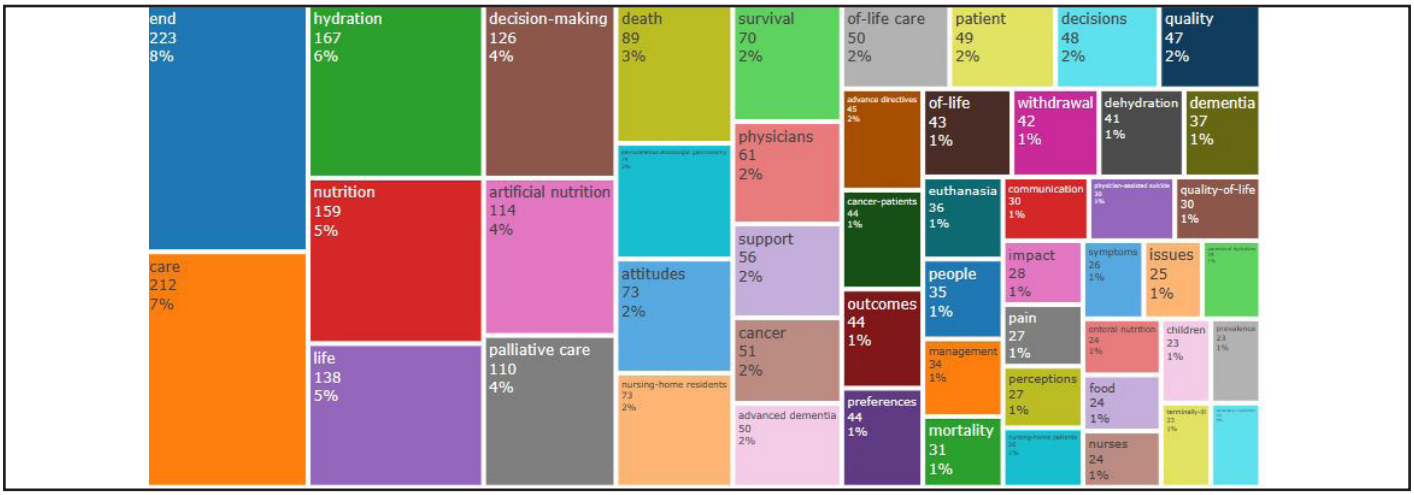

Figure 6a. Tree map

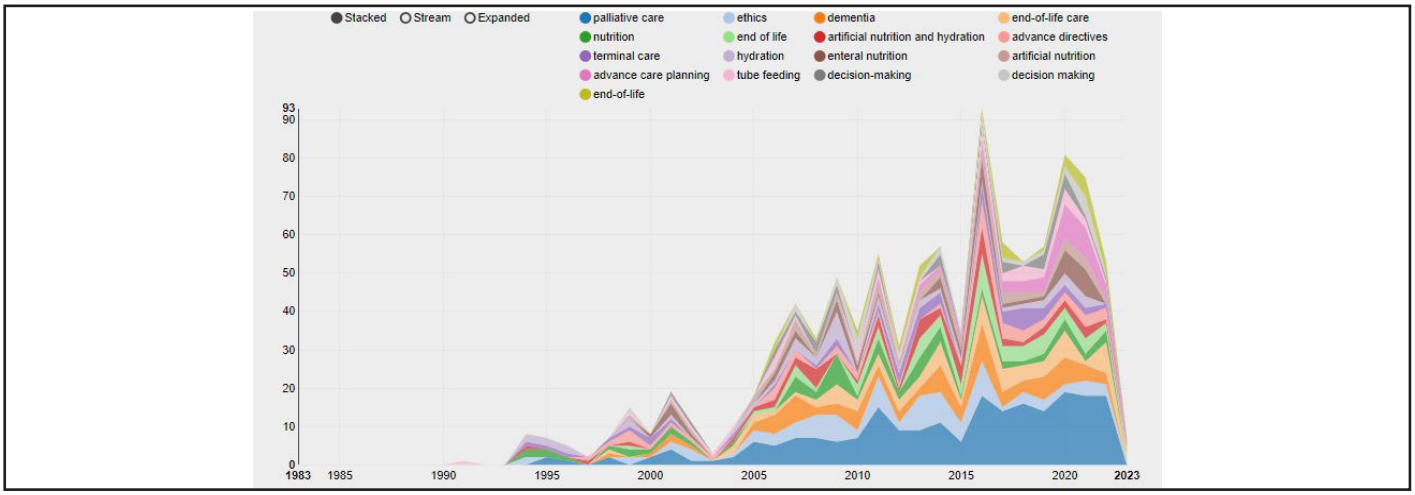

Figure 6b. Keywords by years

DISCUSSION

Bibliometric analysis, one of the most popular mathematical statistics-based methods can evaluate productivity in academia, outline academic frontiers and areas of focus, and project advancement in science trends in the field of study using databases of scientific literature and metrological characteristics. Other methodologies, such as standard reviews, meta-analyses, or experimental studies, are incapable of providing the same level of detail [11]. Furthermore, bibliometric analysis can assess the qualitative and quantitative contributions and collaboration of various countries, journals, institutions, etc. In a variety of medical disciplines, bibliometric evaluations have so far been conducted to give an overview of cross-sectional and longitudinal scientific activity [12-16]. In this study, a specific methodology of combining bibliometric tools was applied to examine the state of research topics in the field of palliative nutrition over time. The analysis revealed not only the most studied clusters of themes but also transnational network connections. We think there is a possibility to further integrate collaboration between organizations active in the field to accelerate research development, knowledge sharing and dissemination, and collaborative fund acquisition. Moreover, using a visualization of keywords in the set of publications (thematic analysis), we explored four main research clusters in the field.

Traditional reviews and meta-analyses have been undertaken in recent years to carefully analyze nutrition research from diverse perspectives. Also, there are some published studies on nutrition [17-20] and nutrition in pediatric intensive care [21]. But no similar study has been published on nutrition in palliative care. Iping et al. [21] searched the Web of Science database too. But differently, they used the VOSviewer application to create networks. Through the use of bibliometric techniques, Youn et al. [17] examined the global trends in nutrition in cancer research. VOSviewer was also used in this study's visualization analysis. Wang et al. [22] used two tools in their study, CiteSpace, and VOSviewer, to perform bibliometric analysis. In this study, we used two bibliometric tools (Biblioshiny and bibliometric online application). Our study used a novel technique, to chart the evolution of research teams, partnerships, and areas of interest in the fields of palliative care and nutrition over time. Wang et al. [22] used the Web of Science database as in our study, while Youn et al. [17] used the Scopus database.

Youn et al. [17] pointed out that most of the authors were from European countries. The United States (n = 400), the United Kingdom (n = 101), Italy (n = 68), the Netherlands (n = 61), and Canada (n = 54) were among the countries with the most publications in the current study. We thought that this difference was due to the difference in subject matter between our study and the study of Youn et al. [17].

A recent bibliometric study by Wang et al. [22] examined publications on nutrition in child health. In this study, the top three contributing countries were reported to be the United States, the United Kingdom, and Canada. However, the contribution of developing countries was incredibly small according to this study's results [22]. In this study, there were publications from 59 countries. The United States (n=400), the United Kingdom (n=101), Italy (n=68), the Netherlands (n=61), and Canada (n=54) were among the countries producing the most publications on palliative nutrition. Similarly, the number of publications from developing countries was limited.

In the study by Wang et al. [22], the number of publications showed a decreasing trend after 2016. The annual number of publications in our study has significantly increased over the last 20 years. These publications grew at a 5.34% yearly rate. The two years with the most publications (n: 67, and n: 64, respectively) were 2020 and 2021. From 2003 to 2022, the number of publications fluctuated, but overall they've increased.

According to Wang's study [22], the United States and the United Kingdom both maintain close relations with 55 other countries. These countries were followed by Canada (n: 54) and Switzerland (n: 53) Australia (n: 53) and Belgium (n: 50). The fact that China has alliances with 48 nations was noteworthy, and they reported that China will lead the way in child nutrition in the future. In our study, Germany, the Netherlands, the United States of America, the United Kingdom, and Belgium were the countries with the most multi-country publications. In other words, they were the countries with international collaborations. In our study, the publications were frequently published in journals dealing with geriatrics and palliative care and pain. Journal of Pain and Symptom Management, Journal of the American Geriatrics Society, Journal of Medical Ethics, Journal of Palliative Medicine, and Journal of Palliative Medicine were the journals with the highest number of publications on palliative nutrition. Journal of the American Geriatrics Society was the highest-cited journal.

We also conducted keyword analysis as in other bibliometric studies [23-28]. With the bibliometric methods we used, we also analyzed keyword preferences over the years in detail. According to our results, 'end, care, hydration, nutrition, life, decision-making, artificial nutrition, and palliative care terms were the most preferred keywords.

Limitations

There are some limitations to the current research. First, relying solely on English-language literature may have missed important insights from other languages' literature. Publications in other languages might have gone unnoticed because only English publications were taken into consideration. Because a bibliometric study does not address specific research issues, narrow subtopics are not found. This study's data was also acquired from a single database and focused only on publications in line with the study methodology. Additional studies including comparative or content evaluations of data from other databases can be planned.

CONCLUSION

Overall, the application of modern research technologies enables us to assess and depict broad-scale research trends in the field of nutrition in palliative care, as well as clarify how these results correspond with current publications. The snapshots of the research field can be used to track trends and advances in the network over the next few years. The findings could serve to shape the future research agenda in intensive care nutrition. Citations are another level of bibliometry that is frequently of interest. These might potentially be used to identify certain subjects of interest within the dataset.

Ethics Statement: A public data repository of an electronic database was employed in the current investigation, which was exempt from ethical approval.

Conflict of Interest: The authors has no conflicts of interest to disclose.

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Author Contributions: The authors contributed equally to the preparation of the manuscript.

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Original Research

Global Mapping Analysis of Maxillofacial Trauma Literature From 1980-2022

Yunus Balel [1,2]

[1] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Tokat Gaziosmanpaşa University, Tokat, Turkey
[2] T.R. Ministry of Health, Sivas Oral and Dental Health Hospital, Sivas, Turkey

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Correspondence
Yunus Balel, DDS
Address: Tokat Gaziosmanpasa University Dentistry Faculty Department of Oral and Maxillofacial Surgery, Kaleardı Mahallesi, 60030, Merkez, Tokat, Turkey
E-mail: yunusbalel@hotmail.com

ABSTRACT

Objective: The study is aimed to make a comprehensive bibliometric analysis of the literature in the field of maxillofacial trauma (MFT), to determine the focal points and to present the results in a simplified manner by using various mapping methods. In addition, it is aimed to determine the important articles that constitute the main backbone of the MFT literature with objective methods and to provide a source for education and new studies in this field.

Methods: The publications related to maxillofacial traumas between 1980-2022 using the search terms "injury, trauma, fracture, facial, mandible, mandibular, nasal, midface, orbit, ocular, maxilla, maxillary" were obtained from the Web of Science Core Collection database. Nodes and connections were created using CiteSpace software to create the maps used in the visualization. Cooperation between countries, distribution of topics, co-citation, co-citation clustering analysis were applied.

Results: There were 8850 publications and 78216 references. The MFT literature was divided into a total of 16 clusters. The most published topic was about mandible fractures. While there was a very strong correlation between the country's gross national product and the number of publications (R=0.886), there was a moderate correlation between the country's population and the number of publications (R=0.403).

Conclusion: In the presented study, the forty-years history of the MFT literature was evaluated with bibliometric analysis methods; the most influential publications, the topics in which the literature is divided and hot spots were determined.

Keywords: Maxillofacial trauma; Mapping analysis; Bibliometric analysis

INTRODUCTION

The face, which is the most important structure of individuals' social identities, is a structure consisting of many units responsible for various vital functions. The brain, eyes, nose and jaws are the most important units of this structure [1]. Maxillofacial trauma (MFT) includes any external injury to the hard and soft tissues of the head and face region. Traumas to these areas include abrasion, laceration, contusion, hematoma, rupture, burn, bone fractures, etc. may form [2]. The complexity of the structures found in this region complicates the management of MFTs and concerns professionals from a variety of specialties.

Science, by its nature, is constantly growing. The number of academic publications in the field of MFT has increased, as in many other fields, due to many reasons such as the ease of communication and transportation between countries, the increase in the number of academic journals and the ease of access to these journals. However, determining the impact of a scientific paper can be difficult [3]. Bibliometric analysis is a method of measuring the effectiveness and trends of a discipline by using features such as the number of articles and publications in databases, the number of citations, and the year

of publication. This method helps to assess the popularity of a discipline and the impact of publications in related fields [4, 5]. There were previous bibliometric analysis studies on MFT [6–8]. However, these studies did not have a comprehensive reference and mapping analysis to assess the extent to which the publications contributed to the literature. Science mapping and visualization helps to discover scientific knowledge [3, 4]. In particular, document co-citation analysis enables identification of relevant literature and academic communities as well as societal impacts that may be overlooked in standard approaches to literature review [3, 4, 9].

In this study, it is aimed to make a comprehensive bibliometric analysis of the literature in the field of MFT, to determine the focal points and to present the results in a simplified manner by using various mapping methods. In addition, it is aimed to determine the important articles that constitute the main backbone of the MFT literature with objective methods and to provide a source for education and new studies in this field.

MATERIALS AND METHODS

This study, which is a bibliometric global mapping analysis study, is exempt from ethics committee approval [10]. The search was performed on the Web of Science Core Collection database on 27.12.2022 to avoid bias due to daily database updates. Search settings ([injury] OR [trauma] OR [fracture]) AND ([facial] OR [mandible] OR [mandibular] OR [nasal] OR [midface] OR [orbit] OR [ocular] OR [maxilla] OR [maxillary]) was applied to include search terms and all document types, with a time range of 1980-2022.

CiteSpace software was utilized to generate visual maps depicting nodes and connections. These maps were instrumental in analyzing various elements such as cited countries, journals, and authors. Each node on the map represented an item of analysis, with its size corresponding to the frequency of citation. Nodes were color-coded to denote different years, while the connecting lines between nodes represented co-occurrence or co-citation relationships. The thickness of the lines indicated the strength of the relationship. Co-citation analysis was employed to identify common focal points and hot research topics. Additionally, statistical methods were applied to compare demographic characteristics of countries and the outcomes derived from data analysis. The relationship between the two quantitative data was evaluated with the Pearson Correlation test. Calculated correlation (r) between two variables: a value of r less than 0.20 and values close to zero indicates a very weak relationship; a value between 0.20 and 0.39 suggests a weak relationship; a value between 0.40 and 0.59 indicates a moderate relationship; a value between 0.60 and 0.79 signifies a high level of correlation; if the value is between 0.80 and 1.0, it is interpreted as a very high correlation.

Main Points;

- The United States was the leading country with the highest number of publications and citations.
- The most published topic was about mandible fractures.
- The maxillofacial trauma literature was divided into a total of 16 clusters.
- While there was a moderate correlation between the number of publications and the population, there was a very strong correlation between gross national product.

RESULTS

General Outputs

There were 8850 publications and 78216 references. Although there were some fluctuations during the study period, the annual logistic growth rate of the number of publications was 4.05%.

Cross-Country Cooperation

There were 122 nodes and 482 connections in the cooperation network between countries (Figure 1). The size of the circles represents the number of co-citations, while the red circles inside the circles represent the citation bursts. The United States was the country with the most publications with 4863 publications, followed by India (629), England (562), China (426) and Germany (354).

The relationship between the number of publications and the country's population and the country's gross national product (GDP) was evaluated with the Pearson Correlation test. While there was a moderate correlation (R=0.403) between the number of publications and the population, there was a very strong correlation (R=0.886) between GDP.

Subject Distribution

Mandible fractures (37.36%) were the most common topic. This was followed by Orbital (25.77%), Facial (25%), Cranial (10.46%), Maxillary (6.07%), Mandibular Condyle (3.26%) and Cervical Spinal (0.35%) traumas. The subject distribution of the

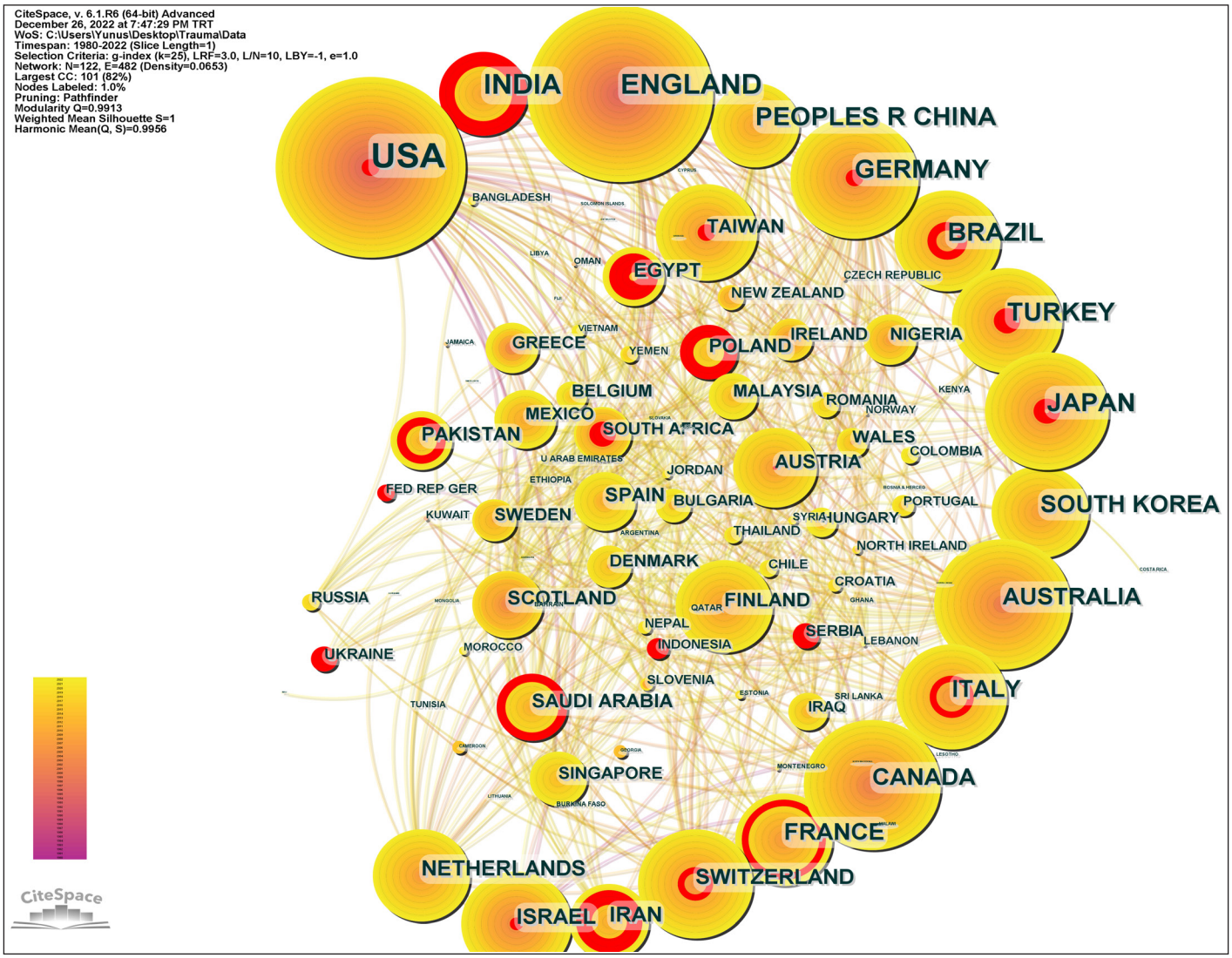

Figure 1. Cross-country cooperation map.

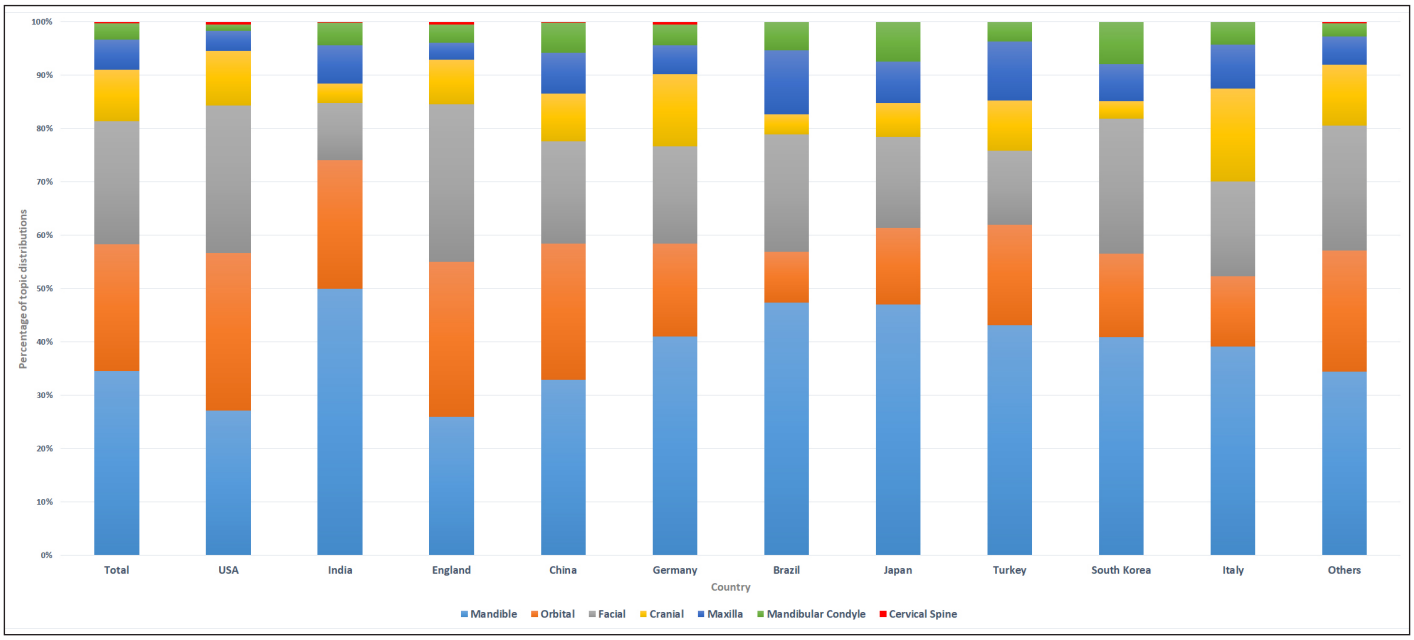

Figure 2. Subject distributions according to fracture localization.

publications of the top 10 countries with the highest number of publications is shown in Figure 2.

Co-citation Analysis

Figure 3 illustrate the co-citation network pertaining to MFT publications. In this visual representation, the nodes correspond to the cited references, while the links between the nodes indicate shared citation relationships. Following the completion of co-citation analysis, a total of 1590 nodes and 5272 connections were identified (Figure 3).

The most cited publication was Mansour-Robaey et al.[11], with 670 citations. The largest radius reference (most co-cited publication) in the network was that of Champy et al [12], with 312 co-citations. The highest citation burst was for Rowe's publication[13] and had a duration of 11 years. The top 10 articles that are most cited, most co-cited, and that have the strongest citation burst are summarized in Table 1.

Co-citation Cluster Analysis

Cluster analysis is mapped in Figure 4. The timeline format of the cluster analysis is shown in Figure 5. As a result of this analysis, it was seen that the MFT literature was formed under 16 main cluster headings. Clusters from largest to smallest are labeled from 0 to 17. The largest cluster was related to mandibular angle fracture, followed by mandibular condylar fracture, pediatric facial fracture and ocular trauma. Cluster labels were determined according to Log-likelihood ratio (LLR), Latent Semantic Indexing (LSI) and Mutual information (MI), and the characteristics of the clusters are summarized in Table 2.

DISCUSSION

Although scientific articles are in the past tense from the time they were published, citations to these articles form the basis for future new publications. They also serve as a source for new articles, training and treatments in the field. By making a detailed analysis of the scientific literature in a particular field, the progress of that subject over time can be followed and the future path of the literature can be predicted [3, 4]. In this study, a bibliometric analysis of the MFT literature was made and it was aimed to make the analysis results simple and easy to understand with the maps created.

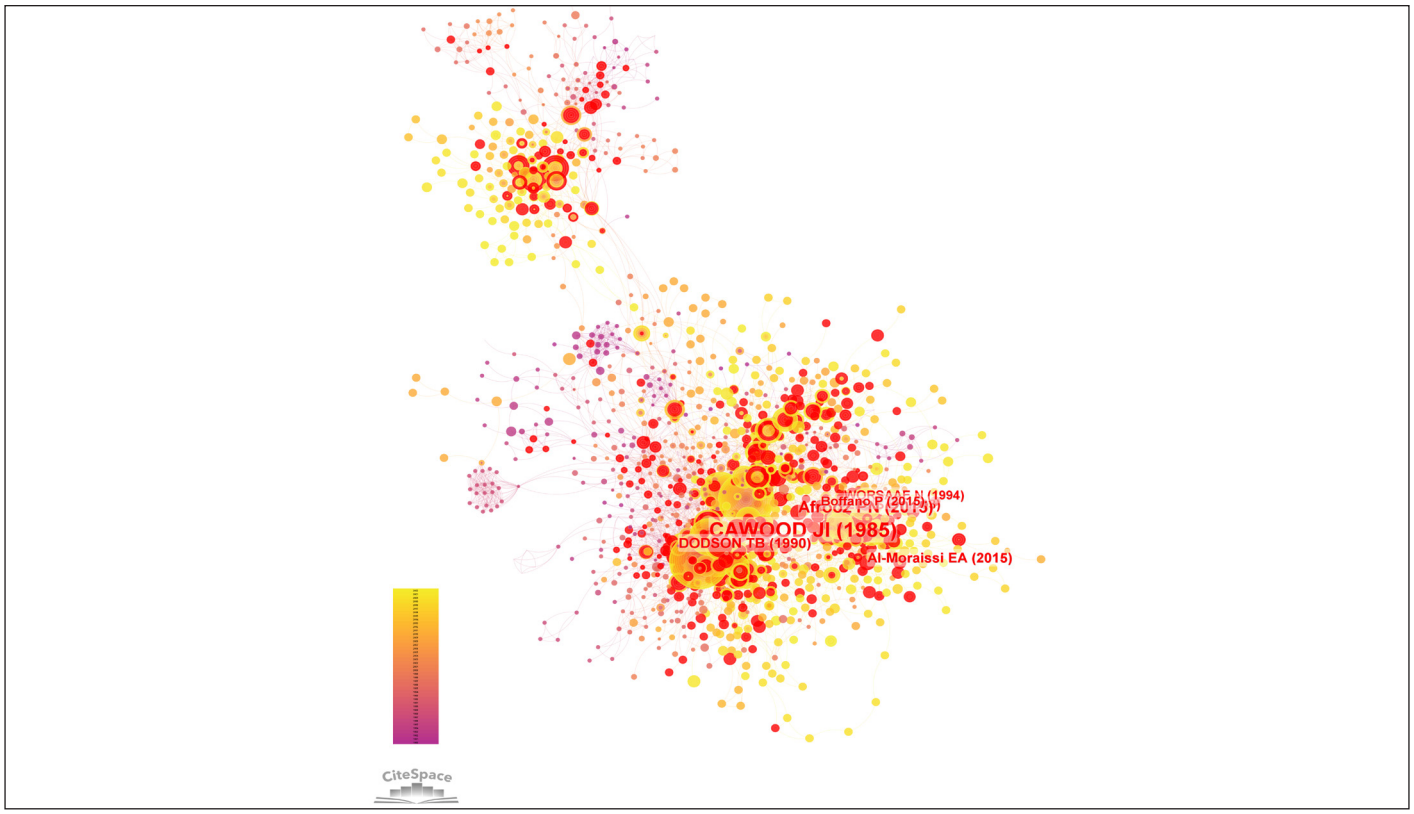

Figure 3. Co-citation analysis map. Each node represents references. Node size is directly proportional to the amount of co-citation. The greater the relationship between the two nodes, the thicker the connecting line. The red circles around the nodes represent the citation explosion.

Table 1. Top 10 articles with the highest metric values

Top 10 Most Cited Articles		Top 10 Co-cited Articles		Top 10 Articles with the Strongest Citation Bursts		
Count	**References**	**Count**	**References**	**Year Range**	**Strength**	**References**
670	Effects of ocular injury and administration of brain-derived neurotrophic factor on survival and regrowth of axotomized retinal ganglion cells (8)	312	Mandibular osteosynthesis by miniature screwed plates via a buccal approach (9)	1988-1999	24.56	Small plate osteosynthesis of mandibular fractures (20)
385	Ten years of mandibular fractures: an analysis of 2137 cases (21)	257	Ten years of mandibular fractures: An analysis of 2137 cases (21)	2018-2022	20.28	The Epidemiology of Mandibular Fractures in the United States, Part 1: A Review of 13,142 Cases from the US National Trauma Data Bank (22)
292	A standardized classification of ocular trauma (23)	146	Cranio-maxillofacial trauma: a 10 year review of 9,543 cases with 21,067 injuries (24)injury surveillance and research data describe the whole spectrum of injuries. The goal of this study was to assess the effect of the five main causes of accidents resulting in facial injury on the severity of cranio-maxillofacial trauma. PATIENTS AND METHODS: During a period of 10 years (1991-2000	1991-1999	17.19	Fixation of mandibular fractures: A comparative analysis of rigid internal fixation and standard fixation techniques (25)
258	An epidemiologic survey of facial fractures and concomitant injuries (1) age and sex of the patients, cause of injury, and associated systems injuries are presented. The majority of facial fractures were found in males; the most prevalent age range was 16 to 30 years. Mandible fractures outranked zygomatic and maxillary fractures (6:2:1	139	The global impact of eye injuries (26) the available information on eye injuries from an epidemiological and public health perspective has been extensively reviewed. This collection of data has allowed an analysis of risk factors, incidence, prevalence, and impact of eye injuries in terms of visual outcome. However, most of the estimates are based on information from More Developed Countries (MDCs	2017-2022	16.64	Surgical Treatment of Adult Mandibular Condylar Fractures Provides Better Outcomes Than Closed Treatment: A Systematic Review and Meta-Analysis (17)
258	Indications for open reduction of mandibular condyle fractures (27)	137	Osteosynthesis with miniaturized screwed plates in maxillo-facial surgery (28)	1998-2008	16.08	Rigid fixation of mandibular condyle fractures (29)

220	Penetrating ocular injuries. Types of injuries and visual results (30)	130	An epidemiologic survey of facial fractures and concomitant injuries (1)age and sex of the patients, cause of injury, and associated systems injuries are presented. The majority of facial fractures were found in males; the most prevalent age range was 16 to 30 years. Mandible fractures outranked zygomatic and maxillary fractures (6:2:1	2016-2022	15.56	European Maxillofacial Trauma (EURMAT) project: A multicentre and prospective study (31)causes and characteristics of maxillofacial fractures managed at several European departments of oral and maxillofacial surgery over one year. The following data were recorded: gender, age, aetiology, site of facial fractures, facial injury severity score, timing of intervention, length of hospital stay. Data for a total of 3396 patients (2655 males and 741 females
210	Fractures of the mandibular condyle: a review of 466 cases. Literature review, reflections on treatment and proposals (32)	129	Treatment methods for fractures of the mandibular angle (33)	1997-2010	15.26	Surgical versus nonsurgical treatment of unilateral dislocated low subcondylar fractures: A clinical study of 52 cases (34)
201	Open versus closed treatment of fractures of the mandibular condylar process - a prospective randomized multi-centre study (35)	124	Fractures of the mandibular condyle: a review of 466 cases. Literature review, reflections on treatment and proposals (32)	1980-1991	14.99	Fractures of the facial skeleton in children (10)
199	Cortical innervation of the facial nucleus in the non-human primate - A new interpretation of the effects of stroke and related subtotal brain trauma on the muscles of facial expression (36)	122	The Ocular Trauma Score (OTS) (37)	2008-2015	14.85	Pediatric facial farctures: Evolving patterns of treatment (38)
190	Pediatric facial fractures: evolving patterns of treatment (39)location and pattern of facial fractures, pattern of facial injury, soft tissue injuries, and any associated injuries to other organ systems were recorded, and fracture management and perioperative complications reviewed. The study population consisted of 137 patients who sustained 318 facial fractures. Eighty-one patients (171 fractures	119	Open versus closed treatment of fractures of the mandibular condylar process–a prospective randomized multi-centre study (35)	2016-2022	14.54	What Method for Management of Unilateral Mandibular Angle Fractures Has the Lowest Rate of Postoperative Complications? A Systematic Review and Meta-Analysis (15)

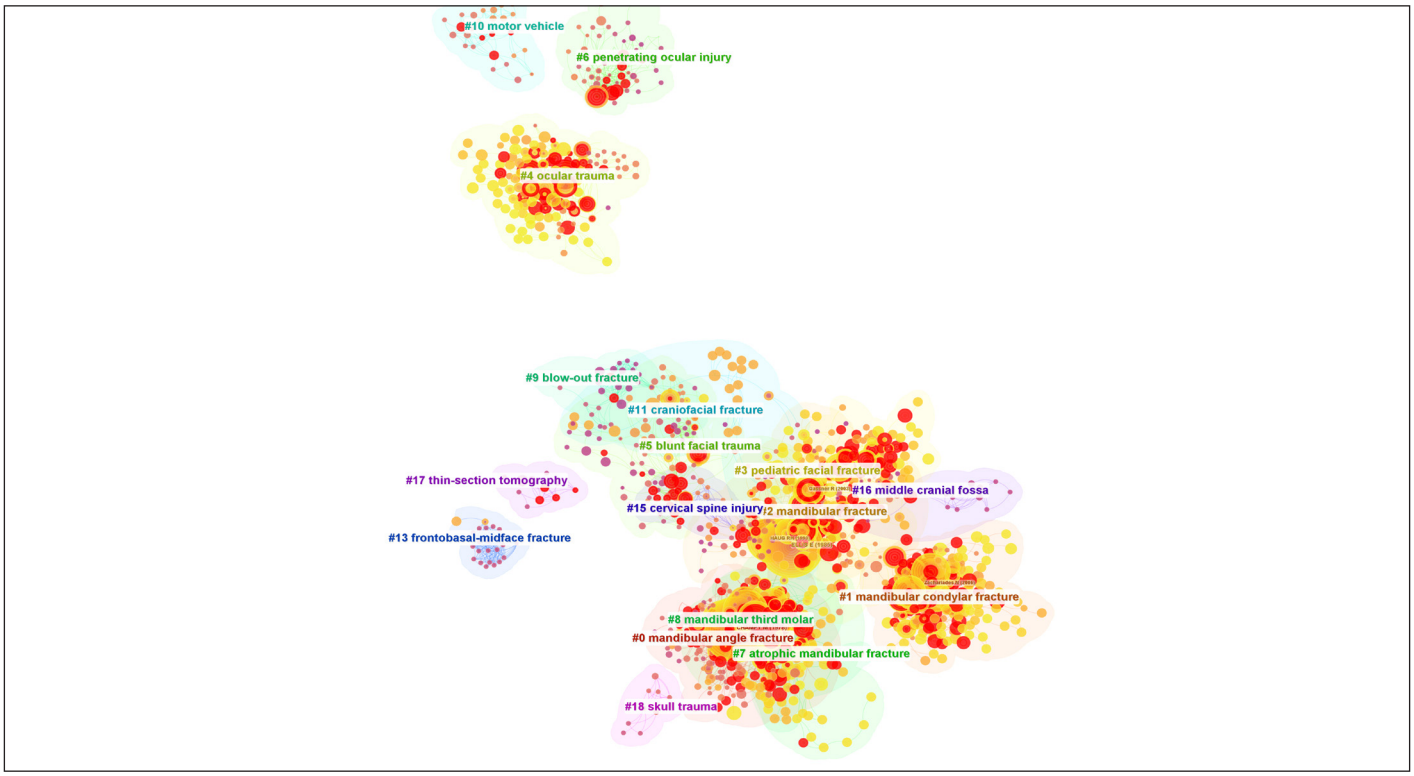

Figure 4. Co-citation cluster analysis map

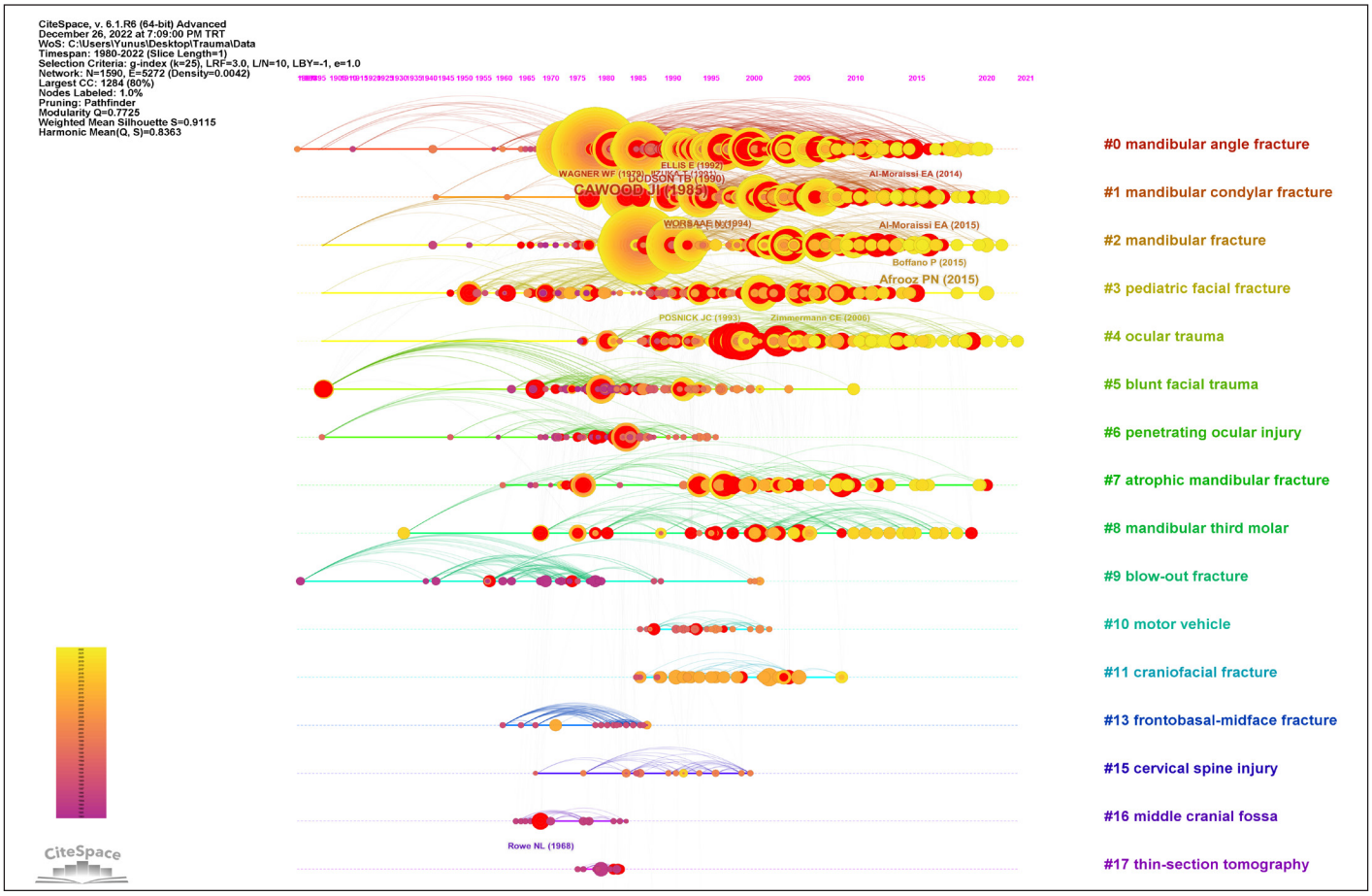

Figure 5. Co-citation cluster analysis timeline map

Table 2. Clusters into which the craniomaxillofacial trauma literature is divided, silhouette values of clusters, size of clusters, labels of clusters (according to LSI, LLR, and MI), and main articles of clusters

Cluster ID	LLR	LSI	MI	Size	Silhouette	The major citing article of the cluster
#0	mandibular angle fracture	mandibular angle fracture	facial plastic-surgery (3.43)	264	0.851	Fixation of mandibular angle fractures: clinical studies (40)
#1	mandibular condylar fracture	mandibular condyle fracture	facial plastic-surgery (1.76)	174	0.954	Does the surgical approach for treating mandibular condylar fractures affect the rate of seventh cranial nerve injuries? a systematic review and meta-analysis based on a new classification for surgical approaches (41)
#2	mandibular fracture	mandibular fracture	facial plastic-surgery (3.14)	160	0.872	Facial fractures in children and adolescents: a retrospective study of 3 years in a hospital in belo horizonte, brazil (16)
#3	pediatric facial fracture	pediatric facial fracture	paediatric mandibular condylar fracture (0.49)	140	0.874	Pediatric facial fractures: recent advances in prevention, diagnosis and management (42)
#4	ocular trauma	ocular trauma	multi-center cross-sectional study (0.91)	128	0.963	Epidemiology of severe ocular trauma following the implementation of alcohol restrictions in far north Queensland (43)
#5	blunt facial trauma	facial fracture	mini-fragment bone plate (0.1)	103	0.844	High-resolution ct analysis of facial struts in trauma .2. osseous and soft-tissue complications (44)
#6	penetrating ocular injury	penetrating ocular injury	mandibular fracture (0.08)	58	0.989	Vitrectomy in severe ocular trauma (19)
#7	atrophic mandibular fracture	mandibular fracture	fractured atrophic edentulous mandible (0.14)	51	0.935	Complications of locking and non-locking plate systems in mandibular fractures (45)
#8	mandibular third molar	mandibular angle	mandibular fracture (0.06)	40	0.955	Do mandibular third molars play a role in fractures of the mandibular angle and condyle? (46)
#9	blow-out fracture	blow-out fracture	mandibular fracture (0.09)	30	0.984	Another look at blow-out fractures of the orbit (47)
#10	motor vehicle	motor vehicle	mandibular fracture (0.09)	27	0.99	Do motor vehicle airbags increase risk of ocular injuries in adults? (48)
#11	craniofacial fracture	craniofacial fracture	mandibular fracture (0.09)	27	0.987	Surgical strategy for complex craniofacial fractures (2)
#13	frontobasal-midface fracture	subcranial management	mandibular fracture (0.09)	23	0.997	The surgical one-stage management of combined cranio-maxillo-facial and frontobasal fractures - advantages of the subcranial approach in 374 cases (49)
#15	cervical spine injury	subcranial management	mandibular fracture (0.09)	14	0.969	Prevalence of cervical spine injuries in patients with facial trauma (50)
#16	middle cranial fossa	middle cranial fossa	mandibular fracture (0.09)	12	0.996	Mandibular condyle fracture and dislocation into the middle cranial fossa (51)
#17	thin-section tomography	facial trauma	mandibular fracture (0.09)	11	0.999	Computed-tomography and thin-section tomography in facial trauma (52)

There is no direct relationship between GNP and facial trauma, but depending on a country's economic situation and access to health services, access to facial trauma treatment and the quality of treatment may vary. For example, in countries with low GNP access to healthcare may be limited and thus facial trauma treatment may also be affected. Likewise, countries with high GNP may have better access to health care and better treatment opportunities. Therefore, there may be an indirect relationship between GNP and facial trauma. As a result of our analysis, there was a very strong correlation (R=0.886) between GNP and the number of MFT publications in countries. This does not necessarily lead to the conclusion that countries with high GNP have a large number of MFTs, but it does indicate that these countries allocate higher treatment and research budgets for the treatment of MFTs.

It is difficult to say that there is a direct relationship between the rate of facial trauma and the population of the country. The facial trauma rate is calculated based on the percentage of the country's population of the number of facial traumas that occur in a country. This rate may differ between countries and may be affected by various factors [14]. The reason for the moderate correlation (R=0.403) between the number of MFT publications and the country population in this study may be that the incidence of facial trauma is affected by the country population in two ways. For example, a high rate of facial trauma in a country may be caused by reasons such as high traffic density, high speed limits, and lack of road safety in the country. At the same time, the low rate of facial trauma may be due to the effectiveness of road safety improvement efforts in the country.

Tahim et al. [6] published a bibliometric analysis of the 100 most cited articles on facial trauma in 2016. The distribution of facial trauma subjects reported by Tahim et al.[6] was similar to that in our presented study, with mandible and orbital fractures being the most common subjects. Our study, which is presented differently from this study, includes co-citation analysis, cluster analysis, citation burst analysis, cross-country collaboration analysis and mapping of these analyzes.

Co-citation refers to the frequency with which two documents are jointly cited by other documents [4]. When two documents are cited together in at least one other document, they are considered to have a shared citation. Typically, commonly cited publications tend to cluster around specific topics [3, 15]. Co-citation cluster analysis plays a crucial role in identifying concentrated areas of research within a discipline and determining influential studies. Moreover, this method enables the examination of the evolution of research within a discipline and aids in predicting its future direction. It encompasses various aspects such as co-citation cluster analysis, research methods, data collection, and analysis. By investigating the relationships and mutual influence among research studies in a discipline, this method sheds light on the factors shaping scientific development [3, 4]. Using Citespace, an automatic clustering of co-cited publications was conducted, revealing that the MFT literature was categorized into 16 main topics. The silhouette metric is employed to assess the uncertainty associated with determining the nature of a cluster. Ranging from -1 to 1, the silhouette value [15] represents the level of uncertainty that must be considered when interpreting the nature of a cluster. A value of 1 indicates perfect separation from other clusters [16]. In this study, the overall silhouette value was 0.9115, indicating excellent separation within the MFT literature. The modularity Q score was higher than 0.5 (0.7725), suggesting that the network was reasonably divided into loosely coupled clusters (Fig. 3.b-c). Among these clusters, Cluster #5 (LLR: blunt facial trauma LSI: facial fracture) exhibited the lowest silhouette value. The co-citation frequency for nasal, malar, and facial soft tissue traumas within this cluster was insufficient to warrant a separate topic.

When a fracture occurs in the mandible, which is one of the structures most affected by facial trauma, the treatment of this condition may vary according to the nature and severity of the fracture site, and surgical or non-surgical methods are generally used. The number and localization of mini-plates is an important question for the surgeon if open reduction is to be performed to correct the fracture [12, 17, 18]. However, when the citation bursts of the articles are examined, it is seen that the 2014[17] and 2015[19] publications of Al-Moraissi and Ellis, which is a more recent article than the article by Champy et al., are more effective today. When the power of the citation bursts is examined, we predict that these two publications by Al-Moraissi and Ellis will increase their importance in the coming years and will be a reference source for new studies on mandible fractures.

Ocular traumas have an important place among facial traumas because the eyes are an important sensory organ for humans and serious consequences such as vision loss can occur as a result of eye injuries [20, 21]. When the trauma localizations constituting the MFT literature were examined, 25.77% were related to ocular traumas when analyzed according to the cluster analysis

of co-citations. These articles were mainly concerned with the etiology, classification and treatment of ocular traumas.

The selected keywords did not include any related to cervical spinal traumas, but 0.35% of the publications were related to spinal traumas. The cervical spinal traumas identified in our analysis were only those that occurred together with MFTs. This demonstrates the severity of MFTs and the areas it affects. However, a gap in the literature is the lack of research on subjects such as brain traumas that may occur after MFTs. This situation could be due to two reasons. The first possible reason is that brain traumas in MFTs have been studied so little that they do not form a distinct cluster. The second possible reason is that brain traumas are reported as completely independent publications from MFTs.

Limitations

This study had several limitations. Only the Web of Science database was used as the database, so not all of the MFT literature from the years mentioned was analysed. However, there were enough articles about MFT in the Web of Science, which has a large database and includes academic journals of certain quality that are constantly updated.

CONCLUSION

In the presented study, the forty-years history of the MFT literature was evaluated with bibliometric analysis methods; the most influential publications, the topics in which the literature is divided and hot spots were determined. The most influential country in this area was the United States. Among MFTs, mandibular fractures were the most studied by the authors, followed by orbital traumas/injuries. MFTs can lead to vital consequences up to spinal traumas, but brain traumas associated with MFTs have not been adequately studied in the literature. It is important to focus on this issue in future studies.

Conflict of interest

The author has no conflicts of interest to disclose.

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Ethical Statement

This study, which is a bibliometric analysis study, is exempt from ethics committee approval.

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Original Research

The Clinical Characteristics and Prognosis of Exon 2 Mutations in Familial Mediterranean Fever

Begüm Avcı[1], Gönül Parmaksız[1], Feride Şahin[2], Aytül Noyan[1]

[1] Department of Pediatric Nephrology, Faculty of Medicine, Baskent University, Adana Dr. Turgut Noyan Training and Research Center, Adana, Turkey
[2] Department of Medical Genetics, Faculty of Medicine, Baskent University, Ankara, Turkey

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Correspondence
Begüm Avcı, MD
Address: Department of Pediatric Nephrology, Faculty of Medicine, Başkent University, Adana Dr. Turgut Noyan Training and Research Center, Adana, Turkey
E-mail(s): begumavci@baskent.edu.tr; begumavcidr@gmail.com

ABSTRACT

Objective: It is unclear whether exon 2 mutations are variations or mutations that causes the disease. This study aimed to evaluate the clinical features and prognosis exon 2 mutations in Familial Mediterranean Fever.

Methods: The clinical features, disease severity and prognosis of all patients with at least one exon 2 mutations were evaluated retrospectively. These data were compared separately for homozygous (Group 1), heterozygous (Group 2), compound heterozygous (Group 3), and complex alleles (Group 4), and the data were compared by grouping patients into those with and without exon 10 mutations.

Results: There were a total of 119 patients with exon 2 mutations, including 11.7% in Group 1, 36.1% in Group 2, 21.8% in Group 3, and 30.2% in Group 4 were similar in terms of demographic data, clinical characteristics, and disease course. When compared patients with exon 10 mutations (+) to those with exon 10 mutations (-), the exon 10 mutations (+) group had a higher presence of chest pain (100%, p=0.02) and a significantly higher mean Pras severity score (6.66±1.87, 6.01±1.40; p=0.02). Additionally, a higher number of patients with exon 10 mutation (-) achieved remission with treatment (76 (67.9%), 36 (32.1%); p=0.03).

Conclusion: Exon 2 mutations have a milder course and higher remission rates but they should be considered as Familial Mediterranean Fever disease because of their similar clinical presentation and response to colchicine treatment with exon 10 mutations. Early treatment and close follow-up should be performed.

Keywords: Genetic variation; mutation; genetic disease, inborn; child

INTRODUCTION

Familial Mediterranean Fever (FMF) is a self-limited, recurrent fever syndrome characterized by attacks accompanied by fever, abdominal pain, chest pain, arthritis or arthralgia, and erysipelas-like rash. It is most commonly observed in Turkish, Jewish, Arab, Armenian, and Italian populations. Mutations in the *MEditerranean FeVer* (*MEFV*) gene are responsible for autosomal recessive FMF [1]. The mutations M694V, M680I, M694I, and V726A in exon 10 of the *MEFV* gene are commonly observed [1, 2]. The R202Q and E148Q mutations in exon 2 are also frequently observed in our country [2, 3]. The disease is clinically diagnosed with the support of *MEFV* gene mutation analysis, especially in atypical cases [4].

In FMF, the repeated episodes of polyserositis are a result of the unregulated secretion of interleukin 1-β due to the mutations

in the *MEFV* gene. The disease's clinical manifestation and progression can differ based on the specific genetic mutations involved. Although the impact of exon 10 mutations on disease symptoms and progression has been extensively studied and established, the influence of exon 2 mutations on the disease remains uncertain. The most commonly observed R202Q and E148Q exon 2 mutations were initially described as genetic polymorphisms. However, increasing studies have shown that patients with these mutations also have similar attack characteristics and disease course to patients with exon 10 mutations [5-7]. There is a continuous inflammation in the subclinical periods, except for the attack periods, and subclinical periods has a significant impact on the course and prognosis of the FMF patients. A good understanding and knowledge of the clinical signs and course of the disease provides early diagnosis and treatment, thus providing a better prognosis and disease course.

The objective of this study is to assess the clinical characteristics and progression of exon 2 mutations and to compare the characteristics of this group with the group carrying exon 10 mutations with exon 2 mutations.

MATERIALS AND METHODS

A retrospective analysis was conducted on the medical records of pediatric patients diagnosed with FMF who received follow-up care at the Department of Pediatric Nephrology in the Baskent University Adana Dr. Turgut Noyan Application and Research Center from 2010 to 2022.

Patients who met at least two of Yalçınkaya et al.'s FMF diagnostic criteria, which include fever lasting between 6-72 hours, abdominal pain, chest pain, and arthritis attacks, accompanied by a family history of FMF, were diagnosed with FMF [8]. In the evaluation of *MEFV* gene analysis in the patients, those carrying exon 2 mutations, whose medical records were accessible and who were monitored for a minimum one year, were included in the study.

Main Points;

- It is unclear whether exon 2 mutations, which most commonly observed in our country, are variations or mutations that cause the disease, FMF.
- Exon 2 mutations have a milder course and remission rates are higher than those with exon 10 variants, however with the similarity of clinical findings and response to colchicine treatment, it should be considered as FMF.
- Clinical suspicion should prompt *MEFV* gene analysis to be conducted to confirm the diagnosis.
- In cases where clinical suspicious findings are supported by the presence of genetic analysis, colchicine treatment should also be initiated for exon 2 mutations.

The genetic analysis of the patients was conducted at the Department of Medical Genetics, Baskent University.After isolating DNA from blood samples in tubes containing EDTA, Reverse Hybridization (RH) assay was performed. Twelve FMF mutations were analyzed by RH assay (FMF StripAssay, Viennalab, Vienna, Austria) kit. A multiplex PCR was performed for each patient to amplify exons 2, 3, 5, and 10 of the MEFV gene. PCR products were then hybridized with test strips using the profiblot T48 (Tecan, Grodig, Austria) system with an appropriate program. Interpretation of results followed the manufacturer's instructions.

Patients carrying mutations of the exon 2 gene were grouped as homozygous (Group 1), heterozygous (Group 2), compound heterozygous (Group 3), and those with complex alleles (Group 4). Age, consanguinity and family history, age when symptoms began, age of diagnosis (start of colchicine), time interval from onset of symptoms (fever, abdominal pain, chest pain, arthralgia, arthritis, myalgia, erysipelas-like rash), acute phase reactants (APRs) during attack-free periods (complete blood count, C-reactive protein (CRP), sedimentation rate, fibrinogen, and serum amyloid A (SAA)), colchicine dose for FMF (mg/day), and clinical findings at the end of the follow-up period were retrospectively evaluated in all patients with exon 2 mutations. Additionally, groups divided according to exon 2 mutation types were assessed based on these datas.

Disease severity was calculated according to the Pras disease severity score, and its adaptation for children by Ozen and colleagues were used [9,10]. Pras criteria, including disease onset age, number of attacks within one month, presence of arthritis, erysipelas-like erythema, and amyloidosis, as well as the colchicine dose, were individually scored and recorded. Patients were then grouped as having mild disease (3-5 points), moderate disease (6-8 points), or severe disease (9 points or above), based on their score values. Patients who have no attacks and no subclinical inflammation under the appropriate colchicine dose were considered in remission. Patients whose colchicine was discontinued, some of them had their medication

stopped by their families due to the absence of complaints. In some of them, colchicine was temporarily suspended by us clinicians in patients who were in remission, as their clinical and laboratory parameters were normal and their families wanted not to continue the medication.

The included exon 2 patients were categorized into two groups based on carrying of exon 10 mutations: those who carried the mutation (exon 10 mutation (+)) and those who did not (exon 10 mutation (-)). Demographic and clinical findings were compared between the two groups, and statistically significant differences were identified.

The study was conducted in accordance with the Declaration of Helsinki and local regulations, and it was approved by Baskent University Institutional Review Board. (Project no: KA22/297) and supported by Baskent University Research Fund.

Statistical Analysis

We conducted statistical analysis using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). For normally distributed continuous variables with p-values greater than 0.05 in a Kolmogorov-Smirnov test or Shapiro-Wilk test (n<30), we reported mean values and standard deviations. For non-normally distributed continuous variables, we reported median values. To compare continuous variables between groups, we used either Student's t-test for parametric values or Mann-Whitney U test for non-parametric values. Categorical variables between groups were analyzed using the chi-square test or Fisher's exact test. Statistical significance was determined at a pre-defined level of $p < 0.05$.

RESULTS

Demographic, clinical characteristics, disease severity, prognosis of the patients with exon 2 mutations

The study comprised 119 patients who had been diagnosed with FMF, of whom 69 were male (58%) and 50 were female (42%). Consanguinity history was present in 16 patients (13%), and a family history of FMF was present in 40 patients (34%). The mean age when symptoms began was 57.45±36.03 months, the mean age of diagnosis was 79.66±37.83 months, and the mean delay in diagnosis was 22.87±26.78 months. Prior to starting colchicine treatment, the number of attacks per month was 1 or fewer in 85 patients (71%), 1-2 attacks per month in 32 patients (27%), and more than 2 attacks per month in 2 patients (2%).

The most common symptom observed during FMF attacks was abdominal pain, which was detected in 102 patients (86%). This was followed by fever in 78 patients (66%) and arthralgia in 31 patients (26%). However, arthritis was observed in 9 patients (8%), chest pain in 5 patients (4%), erysipelas-like erythema in 3 patients (3%), and myalgia in only 1 patient (1%). One patient (1%) had vasculitis (IgA vasculitis) accompanying FMF. During attack-free periods, APRs such as SAA and others were found to be elevated in only 5 patients (4%). The disease severity levels of the patients, as determined by the Pras disease severity score, were mild in 43 patients (36%), moderate in 70 patients (59%), and severe in 6 patients (5%). The mean Pras score for all patients was 6.24±1.60. The doses of colchicine used were 1 mg/day in 108 patients (91%) and 1.5 mg/day in 11 patients (9%). None of our patients used colchicine at a dose of 2 mg/day or higher, colchicine treatment was discontinued in 38 patients (32%) during follow-up. Out of the 38 patients whose colchicine was discontinued, 3/4 of them had their medication stopped by their families, in 1/3 of them, colchicine was temporarily suspended by us clinicians. The mean duration of colchicine use in patients who discontinued colchicine treatment was 29.13±21.42 months. Additional treatments with anakinra and canakinumab were administered to 2 patients (2%) who were categorized as severe according to the Pras disease severity score and continued to receive colchicine treatment. The patients included in the study were followed up for a mean of 52.44±31.16 months, and at the end of the follow-up period, remission was observed in 112 patients (94%). Table 1 presents the demographic and clinical profiles of the patients.

Demographic, clinical features and disease severity, prognosis by exon 2 mutation type: homozygous, heterozygous, compound heterozygous, and complex alleles

When the patients carrying exon 2 mutation were grouped according to the type of mutation, 14 patients (11.7%) were in Group 1, 43 patients (36.1%) were in Group 2, 26 patients (21.8%) were in Group 3, and 36 patients (30.2%) were in Group 4. Table 2 presents the demographic and clinical data of patients categorized based on the type of exon 2 mutation. The groups exhibited no significant differences with regard to demographic data and clinical findings. Among exon 2 mutations, 49 patients (41.2%) had at least one variant of E148Q, 60 patients (50.4%) had at least one variant of R202Q, and 10 patients (8.4%) had both variants.

Table 1. Demographic, clinical characteristics, disease severity and prognosis of the patients with exon 2 mutations

	Patients (n= 119)
Male, n (%)	69 (58%)
Consanguinity, n (%)	16 (13%)
Family history of FMF, n (%)	40 (34%)
Age when symptoms began, month (mean±SD)	57.45±36.03
Age of diagnosis, month (mean±SD)	79.66±37.83
Delay in diagnosis, month (mean±SD)	22.87±26.78
Attack frequency, (before colchicine) <1 times/month, n (%) 1-2 times/month, n (%) >2 times/month, n (%)	 85 (71%) 32 (27%) 2 (2%)
Symptoms during attack Abdominal pain, n (%) Fever, n (%) Arthralgia, n (%) Arthritis, n (%) Chest pain, n (%) Erysipelas like erythema, n (%)	 102 (86%) 78 (66%) 31 (26%) 9 (8%) 5 (4%) 3 (3%)
Pras severity score (Pras) (mean±SD)	6.24±1.60
Pras severity category Mild, n (%) Moderate, n (%) Severe, n (%)	 43 (36%) 70 (59%) 6 (5%)
Colchicine treatment discontinued, n (%)	38 (3%2)
Colchicine usage time (those in whom colchicine was discontinued) (mean±SD)	29.13±21.42
Other treatment, n (%) Anakinra, n (%) Canakinumab, n (%)	 2 (2%) 2 (2%)
Remission, n (%)	112 (94%)
Follow-up period, month (mean±SD)	52.44±31.16

Table 2. Demographic, clinical features and disease severity, prognosis by exon 2 mutation type

	Group 1 (n=14, 11.7%)	**Group 2 (n=43, 36.1%)**	**Group 3 (n=26, 21.8%)**	**Group 4 (n=36, 30.2%)**	**p value**
Male, n (%) Female, n (%)	7 (10.1%) 7 (14%)	28 (40.6%) 15 (30%)	13(18.8%) 13 (26%)	21 (30,4%) 15 (30%)	*0.58*
Consanguinity, n (%)	3 (18.8%)	5 (31.3%)	4 (25%)	4 (25%)	*0.77*
Family history of FMF, n (%)	6 (15%)	13 (32.5%)	7 (17.5%)	14 (35%)	*0.63*
Age when symptoms began, month (mean±SD)	59.21±40.54	59.65±33.78	62.04±41.71	50.81±32.94	*0.61*
Age of diagnosis, month (mean±SD)	77.29±47.32	79.23±35.69	82.77±42.74	78.86±33.92	*0.97*
Delay in diagnosis, month (mean±SD)	17.64±24.61	19.16±25.56	20.38±23.43	27.78±33.76	*0.49*
Attack frequency (before colchicine, n (%)) times/month <1 1-2 >2	 8 (9.4%) 5 (15.6%) 1 (50.0%)	 33 (38.8%) 10 (31.3%) -	 21 (24.7%) 4 (12.5%) 1 (50.0%)	 23 (27.1%) 13 (40.6%) -	*0.18*

Symptoms during attack, n (%) Abdominal pain Fever Arthralgia Arthritis Chest pain Erysipelas like erythema, n (%)	12 (11.8%) 10 (12.8%) 3 (9.7%) 2 (22.2%) 1 (20%) 0	33 (32.4%) 27 (34.6%) 12 (38.7%) 2 (22.2%) 0 1 (33.3%)	23 (22.5%) 17(21.8%) 6 (19.4%) 1 (11.1%) 1 (20%) 0	34 (33.3%) 24 (30.8%) 10 (32.3%) 4 (44.4%) 3 (60%) 2 (66.7%)	0.15 0.24 0.93 0.46 0.29 0.49
Pras severity score (Pras) (mean±SD)	6.93±2.02	5.88±1.12	5.92±1.41	6.61±1.90	*0.05*
Pras severity category Mild, n (%) Moderate, n (%) Severe, n (%)	 3 (7%) 9 (12.9%) 2 (33.3%)	 17 (39.5%) 26 (37.1%) -	 12 (27.9%) 13 (18.6%) 1 (16.7%)	 11 (25.6%) 22 (31.4%) 3 (50%)	 *0.25*
High levels of APRs in the attack free period, n (%)	1 (20%)	1 (20%)	2 (40%)	1 (20%)	*0.65*
Remission n (%)	13 (11.6%)	43 (38.4%)	22 (19.6%)	34 (30.4%)	*0.07*
Follow-up period, month(mean±SD)	62.78±41.44	44.25±26.46	54.54±34.17	56.66±28.54	*0.15*

*APRs: Acute phase reactants

Table 3. Differences between those with exon 10 mutations and those without exon 10 mutations in terms of demographic, clinical characteristics, disease severity and prognosis of patients with exon 2 mutations.

	Exon 10 mutation (+) (n=41)	**Exon 10 mutation (-) (n=78)**	**p value**
Male, n Female, n	23 (56.1%) 18 (43.9%)	46 (59.0%) 32 (41.0%)	*0.76*
Consanguinity, n (%)	6 (14.6%)	10 (12.8%)	*0.78*
Family history of FMF, n (%)	16 (39.0%)	24 (30.8%)	*0.37*
Age when symptoms began, month (mean±SD)	48.1539.89	62.3333.05	*0.30*
Age of diagnosis, month (mean±SD)	76.0941.32	81.5336.01	*0.14*
Delay in diagnosis, month (mean±SD)	27.6135.40	20.3820.75	*0.16*
Attack frequency <1 times/month, n (%) 1-2 times/month, n (%) >2 times/month, n (%)	 25 (61.0%) 14 (34.1%) 2 (4.9%)	 60 (76.9%) 18 (23.1%) 0	 *0.05*
Symptoms during attack Abdominal pain, n (%) Fever, n (%) Arthralgia, n (%) Chest pain, n (%) Arthritis, n (%) Erysipelas like erythema, n (%)	 37 (90.2%) 29 (70.7%) 11 (26.8%) 5 (12.2%) 1 (2.4%) 2 (4.9%)	 65 (83.3%) 49 (62.8%) 70 (89.7%) 0 70 (89.7%) 1 (1.3%)	 *0.31* *0.39* *0.23* ***0.02*** *0.13* *0.23*
Pras severity score (mean±SD)	6.661.87	6.011.40	***0.02***
Pras severity category Mild, n (%) Moderate, n (%) Severe, n (%)	 12 (29.3%) 25 (61.0%) 4 (9.7%)	 31 (39.7%) 45 (57.7%) 2 (2.6%)	 *0.16*
High levels of APRs in the attack free period, n (%)	3 (7.3%)	2 (2.6%)	*0.22*
Remission, n (%)	36 (87.8%)	76 (97.4%)	***0.03***
Follow-up period, month(mean±SD)	57.9534.66	49.5428.97	*0.11*

*APRs: acute phase reactants

Differences between patients with exon 2 mutation carrying exon 10 mutation (exon 10 mutation (+)) and patients without exon 10 mutation (exon 10 mutation (-))

Table 3 presents the demographic and clinical features of both patients with and without exon 10 mutation. In the group of patients studied, those who had a mutation in exon 2 were identified, 41 (34.5%) had exon 10 mutation. All 5 patients who experienced chest pain as an attack symptom were exon 10 mutation (+) (12.2%). This result indicate a significant difference between patients with and without exon 10 mutation (p=0.02). Patients with exon 10 mutation had a significantly higher mean disease severity score compared to those without the exon 10 mutation (6.66±1.87 vs. 6.01±1.40; p=0.02). The number of exon 10 mutation (-) patients who achieved remission with treatment was higher (76 (97.4%) vs. 36 (87.8%); p=0.03). Both groups were similar in terms of gender, consanguinity and family history of FMF, age when symptoms began, age of diagnosis, delay in diagnosis, and duration of follow-up. There was no significant difference between the two groups in terms of frequency of attacks, symptoms other than chest pain during attacks, Pras classification and elevation of acute phase reactants during attack-free periods.

DISCUSSION

Our study showed that patients with exon 2 mutations, which are common in our country, exhibit similar clinical characteristics and disease progression as those with exon 10 mutations, and have high remission rates with colchicine treatment. When exon 2 mutation variants were grouped as homozygous, heterozygous, compound heterozygous, and complex alleles, the groups had similar characteristics. However, in patients with exon 10 mutations, chest pain was more frequently reported, the disease course was more severe, and the remission rate was lower to those without exon 10 mutations.

It is known that more commonly seen exon 10 mutations lead to typical clinical findings and a more severe disease in FMF [11]. Benign variants, which are usually found in exon 2, are thought to not cause typical FMF phenotype [12]. The E148Q mutation in exon 2 has been described as an insignificant polymorphism [13], showing no typical phenotype characteristics and being an asymptomatic variant [14, 15]. However, various studies have shown that especially homozygous forms of this mutation are symptomatic and require colchicine treatment [4, 7, 16-18].

The R202Q mutation, initially identified as a genetic polymorphism in exon 2 and classified as a benign variant in the Infevers database (Infevers (2020). *MEFV* sequence variants [online] website https://infevers.umai-montpellier.fr) [13] has been shown to be regionally common in our country and consistent with the known FMF clinic [6, 19, 20]. In our study group consisting of patients with mutations in exon 2, the R202Q variant was found to be more common; 50.4% of the patients had at least one variant of R202Q, and 41.2% had at least one variant of E148Q.

In our study, which included patients diagnosed with FMF and carrying mutations in exon 2, the mean age when symptoms began was found to be 57.45±36.03 months (4.8±3.0 years), and the mean age of diagnosis (start of colchicine treatment) was 79.66±37.83 months (6.64±3.15 years). Based on data collected from a large population of pediatric FMF cases, similar mean age when symptoms began (5.1±3.8 years) and mean age of diagnosis (7.3±4.0 years) were observed [17]. In our study, the most common clinical findings during FMF attacks were abdominal pain (86%), followed by fever (66%), arthralgia (26%), arthritis (8%), chest pain (4%), and erysipelas-like erythema (3%). Similarly, Öztürk et al. reported the frequency of clinical findings as follows: abdominal pain in 88.2% of patients, fever in 86.7%, arthritis in 27.7%, chest pain in 20.2%, myalgia in 23%, and erysipelas-like erythema in 13.1%. However, in this study, the R202Q variant was not included due to its acceptance as a polymorphism [17]. In our study investigating exon 2 mutations, R202Q was identified as the most common exon 2 mutation variant, and similar clinical features were observed. In Kandur et al.'s study comparing M694V/R202Q and M694V/- heterozygous mutations, like our study, they showed that the R202Q mutation was associated with the inflammatory phenotype of FMF and that typical clinical findings of FMF could be observed in patients [21]. To summarize, our findings suggest that the R202Q variant can lead to a clinical phenotype resembling that of FMF patients carrying exon 10 mutations. Furthermore, our study revealed that colchicine treatment resulted in regression of clinical symptoms, decrease in attack frequency and a high remission rate.

In our study, patients with mutations in exon 2 were categorized according to the specific type of mutation, and the frequencies were found to be 11.7% homozygous, 36.1% heterozygous, 21.8% compound heterozygous, and 30.2% complex alleles. In Arpaci et al.'s study, the frequencies of R202Q mutation homozygous, heterozygous, compound heterozygous, and complex alleles

were found to be 4.05%, 30.13%, 8.94%, and 6.86%, respectively [20]. In contrast to our study, complex alleles were found to be less frequent. Our study evaluated not only R202Q mutations but also all exon 2 mutations.

Although not statistically significant, the average PRAS score in patients with homozygous exon 2 mutation (Group 1), the fact that colchine treatment was discontinued in only one patient (resumed in adulthood follow-up), and the lower remission rate compared to other groups indicate that homozygous variants have a more severe course. In a previous study by Aktaş et al., it was shown that patients with homozygous variants had more severe disease severity and a higher rate of amyloidosis compared to heterozygous and compound heterozygous patient groups [22]. However, in a study that determined the phenotypic characteristics of patients carrying the E148Q mutation, although not statistically significant, compound heterozygotes and those with complex alleles had a higher frequency of abdominal pain, fever, arthralgia, arthritis, myalgia, and chest pain than patients homozygous for E148Q [16].

The comparison of individuals homozygous for the E148Q mutation in exon 10 of the *MEFV* gene indicates that the disease course is milder, and onset is later in E148Q homozygotes [16, 18]. Tanatar et al. revealed that patients with mutations in exon 10 exhibited more frequent chest pain, arthritis, erysipelas-like erythema, relapsing fever, and higher PRAS scores than patients homozygous or heterozygous for the E148Q variant. They also found high levels of APRs in individuals with exon 10 mutations during the asymptomatic period and suggested that the E148Q variant leads to a milder disease course [23]. However, as indicated by the various data patients carrying the prevalent exon 10 mutation, M694V, exhibit earlier onset of symptoms, more frequent attacks, and a higher incidence of chest pain when they also carry variants in exon 2. Previous studies have hinted that the co-occurrence of exon 2 variants in patients with exon 10 mutations could impact the progression of FMF in distinct ways [5]. Our study also showed that patients carrying mutations in exon 2 along with exon 10 mutation variants had a higher incidence of chest pain, higher PRAS scores, and lower rates of remission. The co-occurrence of exon 10 mutations, which are associated with a more severe clinical phenotype, and exon 2 mutations may lead to a worsening of the severity of the latter. Nevertheless, it is important to mention that neither our study nor the study conducted by Endo Y. et al. [5] included patients homozygous for the M694V mutation.

Compared to individuals carrying exon 10 mutations, those with R202Q variants did not show any significant differences in demographic, clinical, or laboratory data based on our statistical analysis [6]. Sönmezgöz et al. reported that R202Q is the most common *MEFV* gene variation observed with M694V mutation and that chest pain is prevalent in individuals carrying this variant [24]. Similarly, Aydın et al. found a lower prevalence of chest pain in patients with E148Q compared to those with exon 10 mutations [7]. In our study, a higher rate of chest pain was observed in patients with exon 2 mutations, including exon 10 mutations.

It has been shown that *MEFV* mutations are associated with other rheumatic diseases; the E148Q variant has been frequently associated with IgA vasculitis (IgAV), and polyarteritis nodosa [18, 25]. In our study group, one patient had coexisting IgAV, and *MEFV* gene analysis was a compound heterozygous with M694V/R202Q/E148Q.

Exon 2 mutations compared with those containing exon 10 mutations, did not show significant differences in other clinical findings, as previously demonstrated in other studies [7, 18].

Limitations

Although our study has limitations such as being retrospective, small sample size and relatively short follow-up period, it is thought that it will contribute to the literature by evaluating the common exon 2 mutations in our country. It is expected that future prospective studies with adequate sample size and follow-up times will further support our findings, in which exon 2 mutations compared also with homozygous M694V variants, which are the most common among exon 10 mutations and are associated with severe clinical course.

CONCLUSIONS

In conclusion, although exon 2 mutations have a milder course and remission rates are higher than those with exon 10 variants, with the similarity of clinical findings and response to colchicine treatment, it should be considered as FMF, and early treatment and close follow-up should be performed. Given the high prevalence of FMF in our country, clinical suspicion should prompt *MEFV* gene analysis to be conducted to confirm the diagnosis. Even if there is no homozygous variant, colchicine treatment should be started in case of carrying exon 10 mutation or exon 2 mutation, and close follow-up with FMF disease.

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Original Research

Moderator Effect of Chronic Disease on the Relationship Between Marriage Adjustment and Satisfaction in Married Couples

Feyza İnceoğlu[1], Esra Porgalı Zayman[2]

[1] Department of Biostatistics, Malatya Turgut Ozal University, Medicine Faculty, Malatya, Türkiye
[2] Department of Psychiatry, Inonu University, Medicine Faculty, Malatya, Türkiye

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Correspondence
Feyza İnceoğlu, Asst. Prof. Dr.,
Address: Alacakapı Neighborhood, Kırkgöz Street, No:70 Battalgazi , Malatya / Turkey
E-mail: feyza.inceoglu@ozal.edu.tr

ABSTRACT

Objective: The purpose of our study is to show how the relationship between marital adjustment and satisfaction will change in cases of chronic disease in either or both spouses of married couples using a multivariate statistical analysis method.

Methods: Marriage adjustment ve marriage satisfaction scales were used. A structural equation modeling - multiple group analysis method was used in the study, which was designed as a relational screening model.

Results: In the study, which included 898 participants, 56.6% of the participants were female and 43.4% were male. The mean age of the participants was 36.94 ± 8.72 standard deviations. First, the relationship between marital adjustment and satisfaction was analyzed using structural equation modeling, and the relationship between the scales was found to be statistically significant (p=0.001). In the model, which was significant and sufficient, the variable of chronic disease was coded on the arrow representing the regression coefficient between the scales, and multiple group analysis was applied. The relationship between marital adjustment and satisfaction was found to be weak among individuals with chronic diseases. The rate of marriage satisfaction explaining marriage adjustment was lower in individuals without chronic disease (R^2=0.16) than in those without chronic disease (R^2=0.10). While ego scores were not significant in individuals without chronic disease (p=0.237), they were statistically significant in individuals with chronic disease (p=0.017).

Conclusion: Chronic diseases has been found to have a significant impact on the relationship between spouses. Many studies have examined the effects of chronic diseases on marriage. However, our study differs from other studies because of the analytical methods used. In the scales, it was determined whether the chronic disease showed a change in the relationship between the scales, not the scores in the chronic disease state.

Keywords: SEM, multiple group analysis, chronic diseases, marriage satisfaction, marriage adjustment

INTRODUCTION

Chronic diseases is necessary to be under control to ensure that individuals can fulfill their duties and responsibilities in personal care without forcing them and to control the progression of the disease [1]. According to a WHO report in 2011, 85% of the deaths in our country in 2008 were due to chronic diseases [2]. Several studies have revealed that chronic diseases have different psychosocial effects on individuals. In the studies carried out, individuals with chronic diseases, such as fear, hopelessness, depression, helplessness, fear of death, and introversion. It is

known that these situations are experienced very frequently, and as a result, the quality of life of individuals is negatively affected [1,3].

Problems or diseaseses experienced by family members also cause adverse effects on other family members. Families support each other throughout their lives. In adverse situations, the assumeer roles in the family will change, and the people who take on the role of caregiver from the members of the family will change. Family oriented approaches play an important role in the definition and progression of diseases. Studies have shown that family oriented care positively contributes to both the functioning of health systems and diagnosis and treatment of the disease process [4]. It has been stated that marriages are negatively affected by chronic diseases and physical or mental disorders in any of the spouses, and marital adjustment will be damaged [5].

Marriage which is the smallest structural unit of society, is defined as an institution that consists of spouses forming a partnership by sharing responsibilities and a contract on the bond between the spouses [6].

Marital adjustment and satisfaction appear to be concepts used interchangeably. Marital satisfaction: This is the evaluation of the mutual benefits and harms as a whole that spouses have good psychology during the continuation of marriage [7-8]. Marital adjustment: This is defined as the ability of spouses to solve problems together and live with strong communication [9]. As a result of the physical and mental reflection of harmony in marriages to individuals, their quality of life increases, positive effects are observed in their general health status, and life satisfaction increases [10-11]. Quality marriage has positive effects on the happiness of individuals. The most important determinant of happy and healthy marriages is ensuring marital satisfaction. Marriage satisfaction will also increase in individuals who provide marital satisfaction, their quality of life and their support for each other will increase [12].

A significant number of studies in the literature have examined roles of marriage's satisfacion and adjustment. The main issue covered in this study is how the relationship between marital adjustment and satisfaction changes in the case of chronic diseases. Considering that considering the issues chronic diseases has a moderator effect on marital satisfaction and adjustment, a multi-group analysis using structural equation modeling (SEM) was applied. The most important feature of the analysis is that the presence of chronic disease was entered into the expressions representing the basic relationships between the variables (arrows showing the regression coefficients), and the disease was included as a moderator variable in the regression model. SEM is a multivariate analysis method that allows the examination of complex data, examines the indirect and direct effects between observable and unobservable variables, uses multiple regression equations simultaneously, presents the models established between the data visually, includes error terms in the model, and explains the covariance structures between the variables [13-15].

Main Points;

- Chronic diseases may have negative effects on marital satisfaction and adjustment.
- Marriage satisfaction and adjustment of individuals whose self-esteem is affected by chronic diseases may also deteriorate.
- Using multiple group analyses as an alternative to parametric univariate analyses minimized losses in data interpretation.

MATERIAL AND METHODS

Type of Research and Hypotheses

A relational screening model was used to design this study. The preferred model for examining the multifaceted relationships between variable sets provides an opportunity to examine indirect and direct effects [16].

The working hypotheses are as follows:

- H_1: The effect of marital adjustment on marital satisfaction is statistically significant.
- H_2: The moderating effect of chronic disease on marital adjustment and satisfaction is statistically significant.

Place and Time of Research

Data were collected face-to-face and via Google Forms from individuals married for at least three years between January and May 2023. At the stage of obtaining data, the forms were limited to receiving only one answer from each participant. The cookies and IP addresses were checked to determine the reliability of the data.

Sample Selection and Number of Samples

Although there is no clearly defined term for SEM, Schumacher and Lomax (2004) stated that there are studies using 250-500 sample sizes [14]. On the other hand, in the SEM analyses, Kline required a sample number of 200 or more [16]. Accordingly, 918 data forms were collected for this study. However, 23 questionnaires were excluded from the study because they did not provide consent. This study included 895 married participants. Participants were selected by voluntary sampling and snowball sampling, which are non-probability sampling methods.

Inclusion and Exclusion Criteria

Being between the ages of 25-50, being married for at least three years, being literate, and completing the questionnaire completely were the inclusion criteria of the study. Partners with chronic diseases that did not require any additional care assistance (diabetes, blood pressure, cardiovascular diseases, rheumatic diseases, asthma, etc.) were included in the study.

Data Collection Tools

Personal Information Form

The form consisting of gender, age, educational status, occupation, socioeconomic status, and chronic disease variables, which will help define personal characteristics, was applied to the participants.

Marriage Satisfaction Scale (MSS)

The scale developed in 2009 consists of 13 items and three sub-dimensions. The internal consistency coefficient of the scale, whose sub-dimensions were family, sexuality, and self, was calculated as Cronbach's α 0.790. As the score obtained from the scale increases, individuals' marital satisfaction also increases [17].

Marriage Adjustment Scale (MAS)

The scale, first developed by Locke and Walles in 1959 [18], was adapted into Turkish by Tutarel Kışlak in 1999. The scale consists of 15 questions and has a single sub-dimension. The low number of items in the scale is one of the most important reasons for its extensive use. The increase in the scores on the scale, which is scored between 0-60, is expressed as an increase in the harmony of the spouses' feelings, economy, friendship, life criteria, and social characteristics. It has been stated that spouses with high scores have high trust in each other [19].

Statistical Analysis

AMOS 24 and SPSS (Statistical Program in Social Sciences) 28.0 programs were used for the analysis. The significance level (p) value was set at 0.05, and the mean, standard deviation, minimum, maximum, number, and percentage values were used as descriptive statistics. Using the AMOS program, Mardia's coefficient was found to be 1.827 [16]. The calculated value was less than eight showed that the data were suitable for multivariate analysis [20]. Multivariate analysis assumptions, homogeneity of variance, multicollinearity, autocorrelation, etc., were checked, and the reliability coefficient was calculated using Cronbach's α. In the first established path diagram, the measurement model in which the MSS score was the independent variable and the MAS score was the dependent variable. Chronic diseases were included in the model as the moderator variable, depending on the significance of the model. A path diagram was established, in which the MSS score was the independent variable and the MAS score was the dependent variable, and SEM analysis was applied. Structural equation Modeling, which is frequently preferred in the analysis of relational screening models, was used in this study [16].

RESULTS

Demographic information of participants are given in Table 1. In study 508 (56.6 %) were female and 390 (43.4%) were male. The age range of the individuals was 25-50 and the mean was calculated as 36.94 ± 8.72 standard deviations and 159 (17.7 %) were primary school graduates, 294 (32.7%) were high school graduates, and 445 (49.6%) were undergraduate or higher graduates (Table 1).

The descriptive statistics of the scores of the individuals included in the study from the scales and subdimensions used in the study are given in Table 2. The MAS Cronbach's α coefficient was 0.817, and the MSS Cronbach's α coefficient was 0.895 (Table 2).

Multiple Group Analysis - SEM

In the first path diagram, the effect of marital adjustment on marital satisfaction was examined. In the model, marital adjustment scale scores represent the independent variable, marital satisfaction scale scores represent the dependent variable, and e1-e4 are residual terms. Scale sub-dimension scores that do not have the effect of confounding factors on the scale total score, which is a latent variable in structural equation modeling

analyzes, are modeled as observed variables and have a direct effect on the scores. The path diagram of the measurement model is shown in Figure 1.

The regression coefficients and significance of the established models are presented in Table 2.

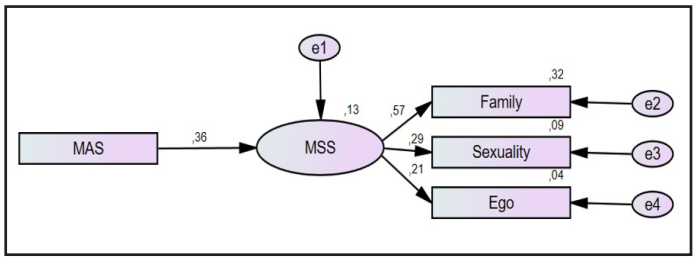

Figure 1. Measurement model path diagram of the relationship between marriage adjustment and marriage satisfaction

In the model; Goodness-of-fit index values obtained as a result of the analysis χ2 (CMIN) 7.794, degrees of freedom (sd) 2, χ^2/ sd 3.897, GFI (Godness of Fit Index, Goodness of Fit Index) 0.996, CFI (Compretive Fit Index, Comparative Fit Index) 0.933, IFI (Incremental Fit Index of Error 0.93), RMSEA (Root Mean Square Root of Approximate Errors) was found to be 0.057 (Table 5).

In the model, 13% (R^2= 0.13) of the MSS score was explained by MAS score. MAS scores had a statistically significant effect on MSS scores (β_1=0.360, p=0.001<0.05, Table 3), and MSS scores also increased depending on the increase in MAS score. In addition, the effects of the MSS sub-dimensions of Family, Sexuality and Ego scores were statistically significant (p<0.05, Table 3).

The established measurement model is statistically sufficient, and the number of samples taken represents the model (Table 5). Since the effects on the measurement model were statistically significant, it was included in the model as a variable with a chronic disease-modulating effect. In the newly established model, the presence or absence of chronic diseases was coded into the path coefficient between the variables, and a multiple group analysis was applied.

Using multigroup analysis, categorical variables consisting of two or more groups that had a moderator effect were included in the model. The main purpose of this study was to determine the role of categorical variables in the relationship between the observed variables. The Critical Z value was interpreted in evaluating the statistical significance of the difference between the groups of the determined categorical variable. The fact that the "Critical Z value," which tests the differentiation in the path coefficients in the groups of the categorical variable, is higher than 1.96, shows a statistical difference for the groups [21]. The path diagram of the established multigroup analysis model is shown in Figure 2.

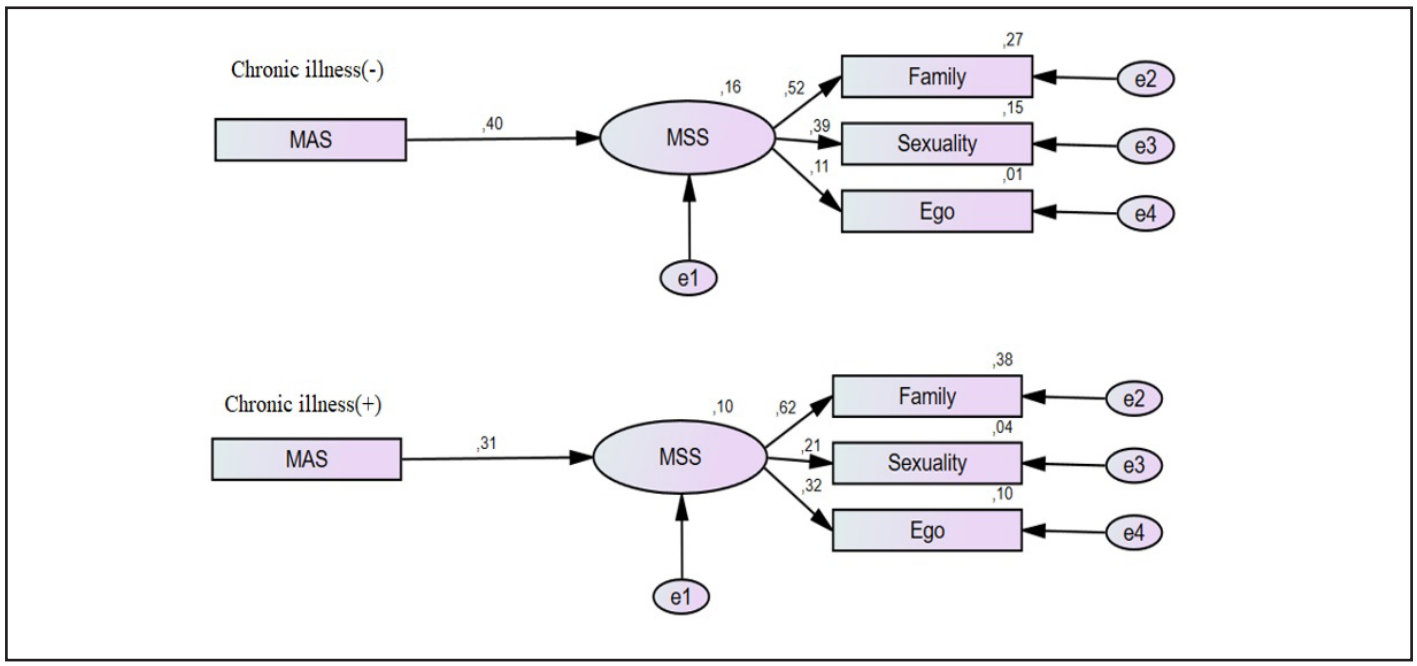

Figure 2. The moderating role of chronic disease in the relationship between marriage adjustment and marriage satisfaction

Table 1. Demographic Information of Participants

Variable	Groups	Frequency	Percent (%)
Gender	Female	508	56.6
	Male	390	43.4
Age	25-30	290	32.3
	31-40	302	33.6
	≥ 41	306	34.1
Education	Primary	159	17.7
	High School	294	32.7
	University and Above	445	49.6
Occupation	No	422	47.0
	Yes	476	53.0
Economical Status	Bad	420	46.8
	Good	478	53.2
Chronic Diseases	No	427	47.6
	Yes	471	52.4
Total		**898**	**100.0**

Table 2. Descriptive Statistics of Scale Scores

Variable	Mean ± sd	(Min - Max)	Cronbach's α
MAS	44.74 ± 5.37	24 - 59	0.817
Family	16.50 ± 3.43	8 - 25	0.895
Sexuality	17.38 ± 3.01	9 - 25	
Ego	10.97 ± 1.94	5 - 15	
MSS	44.85 ± 5.56	26 - 60	

sd; standard deviation

Table 3. Coefficients of Measurement Model Variables

Dependent Variable	Independent Variable	β_1	β_2	p	R^2
MSS	**MAS**	0.360	0.129	***<0.001****	0.13
Family		0.567	1.000	***<0.001****	0.32
Sexuality	**MSS**	0.293	0.453	***<0.001****	0.09
Ego		0.211	0.211	***0.004****	0.04

β_1; Standardized regression coefficents, β_2; Unstandardized regression coefficients, *p<0,05; t test result for the significance of the regression coefficients

A In the newly established model, the goodness of fit index values obtained as a result of the analysis were calculated as χ^2 10,505, sd 2, and $\chi 2$/sd 2.626. The RMSEA value, which is the index showing the adequacy of the sample number, is 0.043, indicating that the sample size is at a very good level for the model used. GFI value of 0.994, CFI value of 0.929, and IFI value of 0.934 were found to be very good in terms of the fit indices of the model (Table 5). The interpretations of the regression coefficients in the path diagram and the "Critical Z value" of the chronic variable are presented in Table 4.

In participants without chronic diseases, 16% (R^2= 0.16) of the MSS score in the model was explained by the MAS score. MAS scores had a statistically significant effect on MSS scores (β_1=0.40, p=0.001<0.05, Table 4), and MSS scores increased depending on the increase in MAS score. In addition, the effect of the MSS sub-dimensions of Family (p=0.001<0.05, Table 4) and Sexuality (p=0.006<0.05, Table 4) scores was statistically significant, but the effect of ego scores was not statistically significant (p=0.237>0.05, Table 4).

In individuals with chronic diseases, 10% (R^2=0.10) of the MSS score in the model was explained by the MAS score. MAS scores had a statistically significant effect on MSS scores (β_1=0.31, p=0.001<0.05, Table 4), and MSS scores also increased with increasing MAS scores. In addition, the effects of the MSS sub-dimensions of Family (p=0.001<0.05, Table 4), Sexuality (p=0.044<0.05, Table 4) and Ego scores were statistically significant (p=0.017<0.05, Table 4).

DISSCUSION

The Cronbach's alpha internal consistency coefficient of the "Marriage Adjustment" and "Marriage Satisfaction" scales are at the desired level [22]. While 427 (47.6%) participants were individuals without chronic disease, 471 (52.4%) were individuals with chronic disease.

A path diagram was established between MAS and MSS, and a measurement model analysis was performed. In the first path diagram established, there was a statistically significant positive relationship between MAS and MSS, and as a result of 1 point increase in MSS scores, MAS scores increased by 0.129 points (β_2=0.129, p=0.001<0.05, Table 3). The measurement model was statistically significant and sufficient, and the fit index values were found at the desired level [20]. Because of the significance of the measurement model, the categorical variable, whether there is a chronic disease, was included in the model. Since the chronic disease included in the model is a variable that has a moderating effect on the relationship between MAS and MSS, the path coefficient was coded according to the presence or absence of disease in the established path diagram, and two different models were obtained. The role, significance, and effect of chronic diseases on the relationship between the scales, and

Table 4. Moderating Role Regression Coefficients in the Relationship Between Marital Adjustment and Satisfaction with Chronic Disease

	Dependent Variable	Independent Variable	β_1	β_2	p	R^2	Critical Z Value
Chronic Diseases (-)	**MSS**	**MAS**	0.400	0.136	***<0.001****	0.16	2.013
	Family		0.522	1.000	***<0.001****	0.27	
	Sexuality	**MSS**	0.391	0.682	***0.006****	0.15	
	Ego		0.105	0.112	0.237	0.01	
Chronic Diseases (+)	**MSS**	**MAS**	0.310	0.119	***<0.001****	0.10	
	Family		0.620	1.000	***<0.001****	0.38	
	Sexuality	**MSS**	0.211	0.289	***0.044****	0.04	
	Ego		0.316	0.293	***0.017****	0.10	

β_1; Standardized regression coefficents, β_2; Unstandardized regression coefficients, *p<0,05; t test result for the significance of the regression coefficients, R^2; Explanatory coefficients

Table 5. Calculated Goodness of Fit Indices for Models

Fit Indexes	Models by Size		Acceptance Ranges		Interpretation
	First	Multiple Groups	Good	Acceptable	
GENERAL MODEL FIT					
CMIN (Chi-Square Goodness of Fit, χ2)	7.794	10.505	The model with the smallest value is chosen.		It measures the similarity of variance and covariance matrices. The model's conformance to the observed covariance structure, as indicated by its structure, is tested.
p	0.001	0.001	p < 0.05		
CMIN / df	3.897	2.626	≤ 3	≤ 4 -5	The low estimated value suggests that the covariance structures are similar. In determining the index, the number of samples is effective. The χ^2 value decreases as the number of samples increases.
COMPARATIVE FIT INDEX					
CFI (Comparative Fit Index)	0.933	0.929	≥ 0.97	0.95 -097	In the absence of latent variables in the model, the independence model compares the covariance matrices of the proposed model. It is sensitive to the number of samples.
IFI (Incremental Fit Index)	0.930	0.934	≥ 0.95	0.94 -0.90	It is obtained by computing the NFI value with df. It eliminates the sample's influence on model calculations.
RMSEA (Root Mean Square Error of Approximation)	0.057	0.043	≤ 0.05	0.05 -0.08	Its goal is to minimize the difference between the observed and estimated covariance matrices. It is sensitive to the amount of samples and may result in the model being rejected if the sample size is limited.
ABSOLUTE FIT INDEX					
GFI (Goodness of Fit Index)	0.996	0.994	≥ 0.95	0.90 -0.95	It is a substitute for the value χ^2. It is calculated independently of sample count. It is also known as the model's sample variance explained. It is comparable to the R^2 value obtained in multivariate regression.

not the scales, were analyzed statistically. Chronic diseases tend to occur, especially in mid-late adulthood and during marriage [23]. Studies on the effect of diseases on marital relationships have shown that the presence of physical diseases in one of the spouses has negative effects on marital adjustment and family functionality [24]. However, this relationship was bidirectional. In other words, marital adjustment can also trigger chronic diseases. It is known that similar lifestyles in couples can be effective in treating chronic diseases [25].

Recently, it has been suggested that marriage is not only related to physical and mental health but also to the relationship between the quality of marriage and health status [26-27]. Studies have shown that high marital satisfaction positively affects couples' physical and mental health. In marriages where marital satisfaction is low, the physical health of individuals may be negatively affected [28-29].

In MSS scores, family ($p=0.001<0.05$, Table 4), sexuality ($p=0.044<0.05$, Table 4), and ego ($p=0.017<0.05$, Table 4) sub-dimensions were statistically significant in those with chronic disease ($p<0.05$; Table 4), but in those without chronic disease, family ($p=0.001<0.05$, Table 4) and sexuality ($p=0.006<0.05$, Table 4) sub-dimensions had a statistically significant effect ($p<0.05$; Table 4), whereas ego sub-dimensions did not have a statistically significant effect ($p=0.237>0.05$; Table 4). Based on these data, it was concluded that self-esteem may be effective in the relationship between marital satisfaction and marital adjustment in the presence of chronic diseases. Self-esteem is a variable associated with marital satisfaction. According to Rosenberg (1979) self-esteem determines an individual's attitude towards himself. Individuals with high self-esteem respected themselves positively. Many factors, such as the long and difficult treatment process of chronic diseases and changes in body image, disrupt the adaptation of individuals [30-31]. This situation can affect self-esteem. Marital satisfaction and harmony of individuals whose self-esteem is affected by chronic diseases may also deteriorate.

In a study conducted with 297 women with heart disease in 2021, it was observed that the support of women from their husbands positively affected their marriage [32]. A study conducted in 2000 showed that marriage had a positive effect on chronic diseases [33]. Waltz et al. Data from 400 men with heart disease and their spouses were collected for five years, and the role of the long-term cognitive effects of diseases in marriage was examined. While supportive marriage environments have positive effects on the health of men in marriages with healthy relationships, negative effects have been found in marriages where adequate social support is not provided between spouses [34].

When the effects of diseases on marriage were examined, it was found that emotional and physical disorders could cause problems in relationships. A health problem in any of the spouses will negatively affect the quality of marriage, and the perception of happiness will decrease among the spouses [5]. In a study conducted in 2014 with the wives of healthy men with Parkinson's, it was observed that the risk of death was higher in women with Parkinson's. The death risk finding, which is one of the most concrete indicators of chronic diseases in marriage, was revealed in the study [35]. In a study conducted by August et al. [36] in 2010, sex and marital status were found to be effective in the management of chronic diseases. In a study conducted using data obtained from 3055 people and their spouses in Korea, Min et al. found that the quality of the relationship and the care of the spouse are effective in alleviating the depression that may be caused by the chronic disease, and the health status of the spouses is related to each other [37].

In our study, the model in which chronic disease has a moderating effect on the relationship between MAS and the MSS was found to be statistically significant and sufficient. The goodness-of-fit indices are at the desired level [20]. A statistically significant difference was found in MAS scores explaining MSS scores between those with and without chronic disease (Critical Z Value=2.013>1.96). The effect of MAS scores on MSS scores was found to be higher in the absence of chronic disease ($\beta_1=0.40$, $p=0.001<0.05$, Table 4) than in the presence of chronic disease ($\beta_1=0.31$, $p=0.001<0.05$, Table 4).

In a statement published by the American Academy of Health Behavior Work Group on Doctoral Research Training in 2005, it was stated that multivariate statistical analysis methods (regression models, generalized linear models, etc.) should be preferred instead of univariate statistical analysis methods (t test, Mann Whitney U test, ANOVA, Kruskal Wallis, etc.) Problems such as data loss and difficulty in interpretation as a result of univariate analyses can be solved by multivariate statistical analysis methods, analyzed and interpreted in unobservable relationships, and researchers will obtain more information about their work [37-38]. In line with this opinion, SEM, a multivariate statistical analysis method, was preferred in

our study. The multiple Gorups analysis method we used was a moderator effect analysis method [21]. SEM shows that the direct and indirect relationships between the variables provide different results for researchers to interpret. In the analysis of error terms, calculations are made by keeping the differences between the sample and estimated covariance matrices at a minimum level, unlike ANOVA and multivariate regression models [14-39]. The model established for the analysis applied in our study and the error terms, relationships between unobservable variables, and change in categorical data in the relationship between the two scales are shown both graphically and mathematically.

Limitations

The limitations of our study; the use of online methods in the data collection system, the unwillingness of married couples to answer some questions, the selected married couples to have been married for at least three years.

CONCLUSION

Our study is the first to include chronic disease as a moderator variable in the relationship between MAS and MSS and to test it using multiple group analysis. For this reason, it will serve as a guide for other studies in this field. The results obtained from the established relationships may differ depending on the sample numbers and structures used in the studies. The reluctance of married couples to answer these questions increased the limitations of the study. As the results of our study may differ between cultures, it will shed light on other studies to be carried out and contribute to the literature.

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Declaration of Competing Interest: The authors have no conflicts of interest to declare.

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Original Research

Turkish Validity and Reliability of the Hikikomori (Social Withdrawal) Scale (HQ-25)

Rabia Kaya [1], Safiye Özgüç [2], Derya Tanrıverdi [3]

[1] Department of Psychiatric Nursing, Harran University, Faculty of Health Sciences, Urfa, Turkey
[2] Department of Psychiatric Nursing, Gaziantep University, Faculty of Health Sciences, Gaziantep, Turkey
[3] Department of Psychiatric Nursing, Gaziantep University, Faculty of Health Sciences, Gaziantep, Turkey

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Correspondence
Derya Tanrıverdi
Address: Gaziantep University, Faculty of Health Sciences, 27310 Gaziantep / Türkiye
E-mail: deryalper@hotmail.com

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ABSTRACT

Objective: This study was conducted to determine the validity and reliability of the Turkish version of the Hikikomori (HQ-25) scale.

Methods: The sample of the study consisted of 418 nursing students. Language and content validity and exploratory and confirmatory factor analysis were used in the validity-reliability analysis of scale. In addition, Cronbach's Alpha coefficient, item-total score correlation, and test-retest reliability methods were used. CFA, it was observed that three-factor structure of scale was preserved in the Turkish sample as well. Significant correlations were found between the scale and other scales ($p<0.01$).

Conclusion: As a result, it was adapted into Turkish, revealing that the scale is valid and reliable in measuring the social withdrawal behavior of individuals. It is recommended to evaluate using the scale in risky groups in terms of social withdrawal.

Keywords: Hikikomori, social withdrawal, validity, reliability, nursing

INTRODUCTION

Social withdrawal is seen with different mental illnesses. Hikikomori is seen as an important problem as it hinders the healing of mental illnesses [1]. Hikikomori, which is expressed as a form of long-term social withdrawal, is seen as a serious problem in terms of both clinical and public health [2]. Hikikomori dates back to the 1970s/1980s in what has been termed "truancy from school" or "school refusal" (futoko). It was then widely accepted as "social withdrawal" or "hikikomori" [3].

Hikikomori is conceptualized as a psycho-sociological condition characterized by prolonged and severe social withdrawal for six months [2]. Teo et al. defined Hikikomori as Spending most of the day at home, avoiding social situations, avoiding social relations with family members, experiencing problems due to social isolation [4,5].

Primary (idiopathic) Hikikomori has been described as well as secondary Hikikomori with psychiatric comorbidity [1,6]. Comorbid psychiatric pathologies are diverse; psychotic disorders, personality disorders, affective disorders, and anxiety disorders are common [6]. Teo et al. determined that hikikomori can be seen together with avoidant personality, social anxiety disorder, and major depression [1]. Hikikomori is known to have a prevalence between 1% and 2% [1]. According to Kato et al., stated that Hikikomori is a latent epidemic in many countries and

should be included in diagnostic systems such as DSM and ICD-11 in the future [7].

There are studies in the literature stating that studies are needed to define the existence of Hikikomori in other cultures and that it is essential to investigate the relationship between Hikikomori and other mental disorders [8,9]. HQ-25 was developed by Teo et al. to assess the severity of hikikomori symptoms over the past six months. HQ-25 is a self-report tool with the new potential to assist in the assessment of a relatively new mental health problem. HQ-25 scale is a new tool to identify individuals in the risk group [2]. In our country, no assessment tool is valid for this mental health problem, which has become an increasing concern. This study was conducted to describe and evaluate the psychometric properties of a scale that allows the assessment of Hikikomori (Social Withdrawal).

MATERIALS AND METHODS

This research was conducted at a state university. Individuals can be selected 5-10 times total number of items in questionnaire [10]. In this direction, when it is calculated by taking ten samples (25*10) for each item, it will be sufficient for 250 people to participate in the research. Similarly, while Tabachnick and Fidell (2001) [11] stated that at least 300 samples were good for factor analysis, Comrey and Lee [12] went for classification and classified 100 samples as poor, 300 samples as good, and 1000 samples as excellent [13]. In this direction, the sample of research consisted of 418 students.

Data Collection Tools

Personal Information Form: The form containing introductory characteristics of individuals was developed by the research team into relevant literature.

The 25-item Hikikomori Questionnaire (HQ-25): HQ-25 was developed by Teo et al (2018) [2]. as a self-administered tool to assess severity of hikikomori symptoms over past 6 months. HQ-25 consists of 25 items. 6 out of 25 questions are reverse scored. HQ-25 has an in score between 0-100. Developers of HQ-25 suggested a cut off score of 42 for the scale. Teo et al. (2018) identified 3 sub-dimensions [14]. These sub-dimensions are Socialization (items 1, 4, 6, 8, 11, 13, 15, 18, 20, 25, 23), Isolation (items 2, 5, 9, 12, 16, 19, 22, 24) and Emotional Support (3, 7, 10, 14, 17, 21) [14].

The Multidimensional Scale of Perceived Social Support (MSPSS): Scale was developed by Zimet et al. (1988) [15]. It was adapted to Turkish society by Eker and Arkar (1995) [16]. In 2001, "Multidimensional Scale of Perceived Social Support Revised" was reviewed by the same authors and internal consistency of MSPSS and subscale scores was found to be acceptable (Cronbach's alpha coefficients = 0.80-0.95) [17]. It is a scale consisting of 12 items.

The Preference for Solitude Scale (PSS): PSS developed by Burger (1995) measures how much people prefer to be alone. The adaptation of scale into Turkish was carried out and evaluated by Erpay and Atik (2019) [18]. It consists of 12 items. One of options in the items reflects preferring to be alone (for example, "I enjoy being by myself"), while the other reflects preferring to be with others (for example, "I enjoy being around people"). When the option of choosing to be alone is selected from the options in the items, this item is calculated as a score [19].

The UCLA Loneliness Scale (ULS-8): The scale was developed internally by Hays and DiMatteo. The adaptation of scale into Turkish was conducted at evaluated by Doğan, Akıncı-Çötok, and Göçet-Tekin. Scores from the scale range from 8 to 32 points. Cronbach alpha was found to be .72. [20].

Research Process

Permission was obtained from scale developers for the Turkish adaptation of HQ-25. For language adaptation, original scale was translated into Turkish by English language experts. Then these Turkish forms were translated back to English and the consistency between Turkish and English forms was examined. Depending on evaluations made by the experts,

Main Points;

- Social withdrawal is a serious concern for mental health professionals and researchers because it is frequently observed in a variety of psychiatric disorders and interferes with recovery.
- There is no validated assessment tool in our country regarding this mental health problem, which is increasingly becoming a source of concern.
- In this study, it was determined that the use of the social withdrawal scale in Turkish society is valid and reliable. This scale is made available to healthcare professionals for use in determining social withdrawal.

necessary corrections were made to questionnaire items. After these opinions, a pre-application was made with 25 individuals with the scale created. After the pre-application, the scale was finalized with the necessary adjustments. The data of the pre-treated group were not included in the study. Pre-application data was not included in the study. After the first application was made to 418 individuals to whom the study would be conducted, the second application was made to 27 individuals 15 days later to evaluate the test-retest reliability.

Data Analysis

Data was analyzed using SPSS 22.0 and AMOS 16 program. In reliability study of HQ-22, item-total score correlation and Cronbach Alpha coefficient and Hotelling's T-Square analysis, and test-retest correlation coefficient were used to reveal its reliability over time. To test validity of HQ-22, content validity index (CVI), construct validity and criterion-related validity studies were conducted. The factor structure of HQ-22 was examined by exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). After Kaiser-Meyer-Olkin (KMO) and Bartlett tests were applied to the suitability of data for factor analysis in construct validity, explanatory factor analysis was performed in SPSS program. After factors were obtained, Eigenvalues statistics and Scree Plot graphics were drawn. The elements were tested with CFA in AMOS program. At this stage, fit indices such as CMIN/DF, RMSEA, NNFI, CFI, RMR, GFI, AGFI, and p-value were used. In the confirmatory factor analysis, the statistics of goodness of fit were evaluated and Path model of questionnaire was given its final form.

In criterion-related validity study, the correlation between Hikikomori (Social Withdrawal) Questionnaire and the MSPSS, the PSS, and ULS-8 scores were calculated with ith Pearson correlation coefficient.

RESULTS

The findings obtained in the research were analyzed under three headings.

1. Introductory Characteristics of the Participants

Participants was determined that 77.5% of them were female, 39% of them were fourth-year students, 88.8% of them lived with their families, and 44% of them rarely left the house for any activity.

Findings Regarding Validity of Scale

Content and Language Validity

The opinions of 8 experts in the field of psychiatry were taken for content validity of scale whose language translation was completed. To say that scale has content validity, the score must be 0.80 and above [10]. In this study, the CVI score was found to be 0.91.

Construct Validity

Factor Analysis

In factor analysis, regardless of its sign, data quality of 0.60 and above is considered high-level quality, and a quality value between 0.30-0.59 is regarded as moderate quality [21].

Exploratory Factor Analysis (EFA)

"Kaiser-Meyer-Olkin"test was used to determine sample adequacy. In addition, "Barlett's Test of Sphericity" analysis was applied to determine whether the scale was suitable for factor analysis. Sample adequacy of Hikikomori Questionnaire, determined by KMO, was found to be 0.919. As a result of the Barlett Test, x^2 was found to be 3051,237. As a result of both analyzes, it was determined to be significant at the $p<0.001$ significance level. In Figure 1, a line graph is presented according to the eigenvalues of the Hikikomori Questionnaire.

Table 1. The distribution of average scores of total and sub-dimensions of the Hikikomori (social withdrawal) questionnaire

Questionnaire	Minimum and Maximum Values That Can Be Taken from the Questionnaire	X	SD
The Hikikomori Questionnaire Total	0-88	35.18	14.54
Sub-Dimensions			
Socialization	0-44	18.08	8.36
Isolation	0-24	10.26	4.12
Emotional Support	0-20	6.83	4.15

***Component Number**: Factor Number

The total score of the scale is 35.18±14.54 (Table 1).

Table 2. The factor matrices (F.M), factor loads (F.L) and data quality (D.Q) of 22 items in the questionnaire

Items			F.M	F.L
The number of the item in the original questionnaire	**The number of the item in the new questionnaire**			
1	1	I stay away from other people.	1	1.00
3	2	There really isn't anyone with whom I can discuss matters of importance.	1	1.00
4*	3*	I love meeting new people.	1	1.36
5	4	I shut myself in my room.	1	1.00
6	5	People bother me.	1	1.80
7*	6*	There are people in my life who try to understand me.	1	0.77
8	7	I feel uncomfortable around other people.	1	1.87
9	8	I spend most of my time alone.	1	0.95
11	9	I don't like to be seen by others.	1	1.91
12	10	I rarely meet people in-person.	1	0.92
13	11	It is hard for me to join in on groups.	1	2.13
14	12	There are few people I can discuss important issues with.	1	0.63
15*	13*	I enjoy being in social situations.	1	1.55
17	14	There really isn't anyone very significant in my life.	1	0.65
18	15	I avoid talking with other people.	1	2.39
19	16	I have little contact with other people talking, writing, and so on.	1	1.35
20	17	I much prefer to be alone than with others.	1	2.24
21*	18*	I have someone I can trust with my problems.	1	0.75
22	19	I rarely spend time alone.	1	-0.53
23	20	I don't enjoy social interactions.	1	2.13
24	21	I spend very little time interacting with other people.	1	0.95
25*	22*	I strongly prefer to be around other people.	1	1.25

Table 3. Confirmatory factor analysis concordance values of the Hikikomori (social withdrawal) Questionnaire (n=418)

Fit Indexes	Normal-Acceptable Fit	Analysis result
Chi-square/df (CMIN/DF)	CMIN/DF ≤3* CMIN/DF ≤5 **	2.53
P-Value for Test of Close Fit	p<.05*	0.000
Root Mean Square Error of Approximation (RMSEA)	RMSEA<0.08**	0.06
Comparative Fit Index (CFI)	CFI value close to or above 0.90 ***	0.89
Root Mean Square Residual (RMR)	0<RMR<0.08*	0.08
Goodness of Fit Index (GFI)	GFI≥0.85*	0.90
Adjusted Goodness of Fit Index (AGFI)	AGFI≥0.85*	0.88

Source: *32, ** 18, ***30

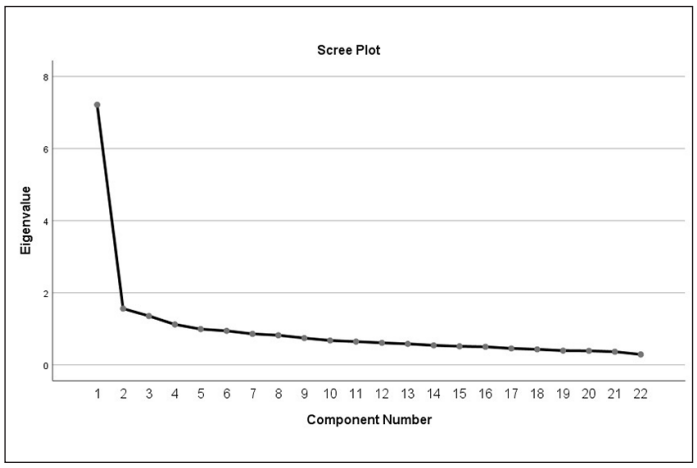

Figure 1. The Scree Plot of the Hikikomori (Social Withdrawal) Questionnaire's Factor Analysis

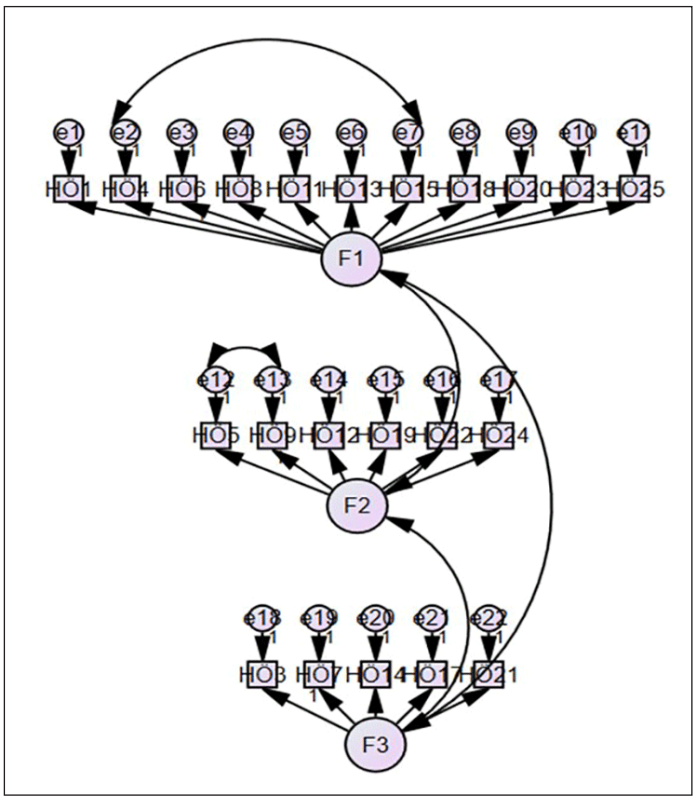

Figure 2. Path diagram and parameter estimates for the Hikikomori Questionnaire

CFA

CFA is applied to test the three-factor structure of Hikikomori (Social Withdrawal) questionnaire. To obtain a stronger structure, the estimation values and items with factor loads below 0.3 in the first measurement (items 2, 10, 16) were removed. CFA was performed on the remaining items. According to this factor analysis, estimates and factor load values of 22 items giving data quality are presented in Table 2. The findings of the goodness-of-fit indices obtained for the CFA are presented in Table 3, and the parameter estimates are presented in Figure 2.

PATH Diagram; As seen in Path, the questionnaire confirmed a three-factor structure and acceptable good fit indices.

It was observed that there was a high rate of covariance (correlation) between the 4th and 8th items and 3rd and 13th items of scale. It was observed that assigning covariance to these items brought the goodness of fit indexes (CMIN/DF, p-value, RMSEA, CFI, RMR, GFI, AGFI) and standardized regression coefficients (estimate) to the desired level, which is vital in CFA.

Criterion Dependent Validity

Within the scope of criterion-dependent validity, Hikikomori (Social Withdrawal) Questionnaire, together with the MSPSS, the PSS, and the ULS-8 were applied to the sample group of 418 people. Correlation values obtained between the scales are presented in Table 4.

A negative correlation was found between Hikikomori Questionnaire and the MSPSS ($r=-0.573$, $p<0.01$); a significant positive correlation was found between Hikikomori Questionnaire and PSS ($r=0.492$, $p<0.01$), and between Hikikomori Questionnaire and the ULS-8 ($r=0.683$, $p<0.01$) (Table 4). According to these results, it was seen that the Hikikomori Questionnaire was valid.

Item Analysis and Reliability

The consistency of the scale within itself (the significance of relationships among the items forming scale) was determined by the Pearson product-moment correlation coefficient. With this coefficient, how much the things that make up the scale contribute to the measurement tool and their relationship with the measurement tool were evaluated.

When the questionnaire's item-total-item correlations and the Cronbach alpha values that occur when items were deleted in Table 5 were evaluated, a very low increase in the Cronbach's alpha value was observed when item 19 was deleted. For this reason alone, removal of the item was not considered.

Cronbach α reliability coefficient of total questionnaire was determined as 0.885 (Table 6). Hotelling's t was 1060,712 ($p=0.000$).

Tablo 4. The Correlation of Hikikomori (Social Withdrawal) Questionnaire with Similar Scales

	1	2	3	4
1. The Hikikomori (Social Withdrawal) Questionnaire	1			
2.The Multidimensional Scale of Perceived Social Support	-0.573**	1		
3. The Preference for Solitude Scale	0.492**	-0.287**	1	
4. The UCLA Loneliness Scale	0.683**	-0.562**	0.204**	1

**p<0.01

Table 5. The Item-Total Item Correlations and Cronbach Alpha Values Resulting When the Items Were Deleted

Items		Item-Total Item Correlation	Cronbach Alpha Value if the Item is Deleted
1	I stay away from other people.	0.341	0.883
2	There really isn't anyone with whom I can discuss matters of importance.	0.564	0.877
3*	I love meeting new people.	0.400	0.882
4	I shut myself in my room.	0.484	0.880
5	People bother me.	0.581	0.877
6*	There are people in my life who try to understand me.	0.451	0.880
7	I feel uncomfortable around other people.	0.570	0.877
8	I spend most of my time alone.	0.490	0.879
9	I don't like to be seen by others.	0.605	0.876
10	I rarely meet people in-person.	0.488	0.879
11	It is hard for me to join in on groups.	0.590	0.876
12	There are few people I can discuss important issues with.	0.405	0.882
13*	I enjoy being in social situations.	0.462	0.880
14	There really isn't anyone very significant in my life.	0.399	0.882
15	I avoid talking with other people.	0.704	0.873
16	I have little contact with other people talking, writing, and so on.	0.659	0.874
17	I much prefer to be alone than with others.	0.624	0.875
18*	I have someone I can trust with my problems.	0.405	0.882
19	I rarely spend time alone.	-0.245	0.899
20	I don't enjoy social interactions.	0.648	0.875
21	I spend very little time interacting with other people.	0.528	0.878
22*	I strongly prefer to be around other people.	0.394	0.882

* Reverse items on the questionnaire

Table 6. Investigation of internal consistency reliability coefficient of total and sub-dimensions of the Hikikomori (Social Withdrawal) Questionnaire (Cronbach Alpha (α))

The Hikikomori (Social Withdrawal) Questionnaire	Cronbach Alpha (α)
Total Questionnaire	0.885
Sub-dimensions	
Socialization	.854
Isolation	.519
Emotional Support	.698

Table 7. The test-retest mean scores according to total and sub-dimensions of the Hikikomori (Social Withdrawal) Questionnaire and correlation analysis

Sub-dimensions		X	SD	r	p
Socialization	Test	18.08	8.36	0,753	<0,001
	Retest	19.11	10.98		
Isolation	Test	10.26	4.12	0,677	<0,001
	Retest	9.96	5.10		
Emotional Support	Test	6.83	4.15	0,861	<0,001
	Retest	5.70	4.79		
Total Questionnaire	Test	35.18	14.54	0,842	<0,001
	Retest	34.77	18.94		

Invariance

Test-Retest Method

The questionnaire's correlation value of total and sub-dimensions of test-retest used to determine the reliability of Hikikomori Questionnaire is indicated in Table 7. It was determined that there was a highly significant relationship in scale and all sub-dimensions between the two measurement results ($p<0.001$).

DISCUSSION

By adopting this scale to Turkish society, it is predicted that it will make a significant contribution to monitoring and correcting the Hikikomori processes experienced by the individuals.

Validity

Three different methods were used to evaluate the validity of the questionnaire. These are content (scope) validity, construct validity (factor analysis), and criterion-related validity.

Content (Scope) Validity of the Questionnaire;

The correlation between the feature to be measured and questionnaire items are related to the validity of scale tool. It is necessary to determine whether the questionnaire item covers the feature that is intended to be measured (content validity) or the power of the item to predict the related construct (construct validity). Consistency/inconsistency between the expert opinions about the questionnaire was also used as an estimation for construct validity [22].

Content Validity Index (CVI) was conducted to evaluate whether each item and the whole questionnaire measure the concept to be measured and whether they contain different concepts. A measurement tool has content validity if it has measured all the features to be measured, and if it is validly measuring every item it covers. For this, the opinions of the relevant experts were taken for content validity. CVI was used as a rating criterion to evaluate expert opinions. In this technique, experts evaluated each questionnaire item by scoring between 1-and 4. To say that questionnaire has content validity, a score of 0.80 and above is expected [23] for questionnaires had content validity.

Factor Analysis

In construct validity, items of the questionnaire should be homogeneous or similar to each other, and best way to evaluate this statistically is factor analysis. Before the factor analysis is carried out to determine to construct validity, the sufficient number of data and their suitability for factor analysis are evaluated [24]. Factor analysis is used for the questionnaires with sub-dimensions other than the total score. The main goal of factor analysis is to determine under which sub-dimensions questionnaire items will be collected. Factor analysis not only tests the integrity of the scale but also helps to clear the subject to be measured from unrelated variables. The purpose of factor analysis is to express a large number of items with a smaller number of factors. Items with a high correlation among themselves constitute factors [25]. Factor analyzes are performed with two different methods, namely EFA and CFA.

Explanatory Factor Analysis

Factor analysis of the sample (Construct validity): First, the KMO analysis was used to determine whether sample size was sufficient. A KMO value close to 1 indicates that data is suitable for factor analysis, while a KMO value below 0.50 is unacceptable [26]. In study, KMO value of the questionnaire was found to be 0.919. These findings showed that sample was suitable and sufficient for factor analysis [27]. According to the result of Barlett's test, x^2= 3051,237 was found to be significant

at a $p<0.001$ significance level. Significance of this finding indicates that sample size is at a good level and correlation matrix is suitable for factor analysis [28].

Eigenvalue (eigenvalue) statistics and a Scree plot graph should be drawn to obtain the factors. The higher the eigenvalue, the higher the variance explained by the factor [28].Three factors with more than 1point eigenvalues were defined.

After examining results of specified explanatory factor structure of model, factors were rotated to interpret the confirmatory factor analysis. For this, the Varimax Rotation process was applied. However, Direct Oblimin and Maximum Likelihood were used as the rotation methods because the number of samples was less than a thousand, and a correlation was expected between the factors [28]. The questionnaire consists of three sub-dimensions as in the original questionnaire.

CFA

In study, CFA was applied to 25 items in questionnaire. The literature shows that λ values above 0.32 are acceptable [11]. To obtain a stronger structure, the estimation values, and items with factor loadings below 0.3 in first measurement (items 2, 10, 16) were removed. CFA was performed on remaining items. Since estimated values and factor loads of items changed with the new CFA, the goodness of fit values of sub-dimensions of the questionnaire were re-examined. Among these fit indices, most commonly used ones are Chi-Square Fit Test, GFI, AGFI, CFI, NFI, RMR or RMS and Root Mean Square of Approximate Errors. Ratio of chi-square value to degrees of freedom (CMIN-DF) is 2 and below 2 shows that the model is good, and 5 and below 5 show at the model has an acceptable goodness of fit [10,30,31]. In this study, ratio of chi-square value to degrees of freedom (2.53) was found to be less than 5. Furthermore the fit indicate CFI valid close to or above 0.90 [30]. RMS the EA value is less than 0.08 [21], GFI and AGFI values being equal to or greater than 0.85 indicate good fit [32] this study, the fit indices were found to be RMSEA= 0.060, RMR= 0.08, GFI= 0.90, NFI= 0.83, AGFI= 0.88, CFI= 0.89. According to findings of the goodness of fit index obtained based on these criteria, it can be said that the three-factor structure of scale was also confirmed in data obtained from Turkish sample.

PATH Diagram: As a result of analyzes made in structural equation model, diagrams called “path diagrams” can be obtained. These diagrams represent graphical representation of the outputs of the model [28,33]. Scale confirmed a three-factor structure and acceptable good fit indices.

Criterion-related Validity

Correlation values of the Hikikomori (Social Withdrawal) Questionnaire were examined with similar scales to reveal the criterion-related validity. The correlation coefficient calculated in this method is expected to be high [10]. There was a negative correlation between the Hikikomori Questionnaire and the MSPSS, a positive correlation between Hikikomori Questionnaire and the PSS, and a positive correlation between Hikikomori Questionnaire and the ULS-8. These results reveal the validity of Hikikomori Questionnaire.

Reliability of the Questionnaire

Internal Consistency

Internal consistency is reliability that determines whether all aspects of the questionnaire are capable of measuring. This criterion method is an analysis that researchers generally use because it gives the result with a single measurement, and it is economical. For a questionnaire to have internal consistency reliability, it is necessary to prove that all sub-dimensions of scale measure same feature [10]. In this study, Cronbach’s alpha internal consistency coefficient, Hotelling’s T Square Analysis, item-total score correlation, and test-retest reliability were examined for internal consistency.

Cronbach’s Alpha Coefficient of Reliability is frequently used as a method of estimating the internal consistency of Likert-type models [34,35]. The most appropriate way to determine that each item of the questionnaire measures the same attitude within itself is to calculate Cronbach’s alpha coefficient [10]. There can be a single α value for each item or an average α value for all items. Cronbach’s alpha internal consistency coefficient is a value found by ratio of the sum of the item variances in the model to the general variance. This value is between 0 and 1. Higher Cronbach alpha coefficient of a scale, it can be said that questionnaire consists of consistent items measuring elements of same feature. The ranges in which the Cronbach’s alpha coefficient can be associated with reliability of questionnaire are expressed as follows in the relevant literature: If it is between $0.00<\alpha<0.40$, the questionnaire is unreliable if it is between $0.40<\alpha<0.60$, the questionnaire has low reliability if it is between $0.60<\alpha<0.80$, the questionnaire has considerable reliability, and if it is between $0.80<\alpha<1.00$, questionnaire has high reliability [24].When the original form of the questionnaire was compared

with the adaptation of the questionnaire to the Turkish samples, it was seen that the findings were similar in terms of reliability (Cronbach's alpha=0.96 for Japan, Cronbach's alpha= 0.89 for Turkey) [2]. In the study in which the questionnaire was developed, the Cronbach's alpha coefficients for sub-dimensions of the scale were found to be 0.94 for socialization, 0.91 for isolation, and 0.88 for emotional support, respectively [2]. In this study, the scale's sub-dimension Cronbach's alpha coefficients were found to be 0.85 for socialization, 0.51 for isolation, and 0.70 for emotional support, respectively. The findings obtained as a result of this research indicated that the scale is a reliable questionnaire due to its high-reliability coefficient and that it is generally similar to the original questionnaire.

Hotelling's T-Square Analysis: In study, Hotelling's T-Square test was used to investigate whether students answered according to their views or under the influence of the researcher and others [25]. Hotelling's T Square was 1060.712 (p = 0.000). It was concluded that difference between the item mean scores was significant, and scales did not show any response bias.

Test-retest Reliability

The test-retest application, which was carried out to determine the reliability of Hikikomori Scale, was applied to participants participating in the research at two-week intervals. The correlation coefficient (r-value) was calculated between the two application scores. This value should approach 1 and be above 0.70 at least [10]. In this study, a high, positive and significant relationship was found between first and second measurement (r= .84, p=0.01).

Item-Total Score Correlation

For an item to be acceptable, the item-total correlation coefficient must be positive and at least 0.20 [10,36,37]. In this study, the item-total correlation of scale was found to be 0.20 and above. Total score correlations of all items were sufficient for item analysis. These findings showed that the model scales have no problematic items in the final version and have internal consistency. When an item was deleted from scale, no item would significantly increase the calculated Cronbach Alpha values.

Limitations

This study, which was conducted to adapt Hikikomori Questionnaire into Turkish, has some limitations. Considering Cronbach's alpha values of questionnaire's sub-dimensions obtained in this study, it is seen that the isolation sub-dimension value is acceptable but low. This limitation can be eliminated by increasing the sample size in other studies to be conducted. The fact that university students constitute the sample creates a limitation in terms of representing individuals in samples consisting of different groups, this limitation can be eliminated by working with different sample groups for future studies.

CONCLUSION

Eventually, the questionnaire consists of 22 items and has three sub-dimensions. These sub-dimensions are Socialization (items 1, 3,5, 7,9,11, 13, 15, 17, 20, 22), Isolation (items 4, 8, 10, 16, 19, 21) and Emotional Support (2, 6, 12, 14, 18). 5 items (3, 6, 13, 18, 22) are reverse scored in the questionnaire. Lowest score that can be obtained from items is 0, and highest score is 4. Score range of scale is 0-88. The increase in total score obtained from scale in the dictates that level of social withdrawal behavior of the individual increases. An increase in the total score obtained from the sub-dimensions of the scale also indicates an adverse increase in the relevant area. This scale, whose validity and reliability studies were conducted, is thought to be a valid and reliable measurement tool for this mental health problem, which has become an increasing concern in Turkey. It is recommended that the social withdrawal scale be used both in individuals with and without a diagnosis of mental illness. In addition, it is recommended to evaluate the effects of Hikikomori on loss of workforce.

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Ethics Committee Approval: Ethics committee approval was received for this study from Gaziantep University Clinical Research Ethics Committee (Approval date: 04.11.2020; approval number: 2020/312).

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Original Research

Berberine Synergizes with Cisplatin via Inducing Apoptosis on A549 non-Small Cell Lung Cancer Cells

Merve Becit Kızılkaya[1], Şeyma Öncü[2], Serkan Şen[3], Sefa Çelik[4]

[1] Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Afyonkarahisar Health Sciences University, Turkey
[2] Department of Medical Pharmacology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Turkey
[3] Department of Medical Laboratory Techniques, Ataturk Vocational School of Health Services, Afyonkarahisar Health Sciences University, Turkey
[4] Department of Medical Biochemistry, Faculty of Medicine, Afyonkarahisar Health Sciences University, Turkey

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Correspondence
Merve Becit Kizilkaya, PhD
Address: Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Afyonkarahisar Health Sciences University, Turkey
E-mail: mervebecit@hotmail.com

ABSTRACT

Objective: Lung cancer is the most common cause of morbidity and mortality. Platinum-based chemotherapy, which is the primary line of treatment, offers limited benefit due to drug resistance and side effects. Berberine (BBR), which is characterised by its potent and safe anticancer activity, represents a promising combination option in chemotherapy. To overcome the limitations in lung cancer chemotherapy, we investigated whether BBR and cisplatin (CIS) exert synergistic effects on non-small cell lung cancer cell line (A549) based on cytotoxicity and apoptotic response markers.

Methods: The potential cytotoxic effects of the combination treatment were evaluated using the MTT and Chou-Talalay methods. Elisa assays were also performed to measure the levels of the pro-apoptotic protein Bax and the effector protein caspase (Cas)-3.

Results: The results showed that BBR alone reduced A549 cell viability in a dose-dependent manner and synergized with CIS (CI =0.34±0.05 at IC50 concentrations). Elisa results showed that the combined treatment (both at IC50 concentrations) modulated apoptotic signalling pathways in A549 cells. Bax and Cas3 protein levels were dramatically enhanced in A549 cells treated with CIS +BBR compared to control (0.5% DMSO) ($p < 0.001$).

Conclusion: Our results suggest that BBR can synergistically enhance the therapeutic effect of CIS in A549 cells. The potential therapeutic efficacy of BBR as part of a combination in current chemotherapy should be supported by in-depth research and clinical studies on the molecular mechanisms associated with cancer.

Keywords: Berberine (BBR), Cisplatin (CIS), synergism, A549, apoptosis

INTRODUCTION

Cancer is one of the diseases with the highest mortality rate in the world [1]. It is predicted that cancer incidence will increase dramatically in the coming years due to demographic changes such as population growth and aging. According to the GLOBOCAN update, an estimated 10 million people will die from cancer in 2020. Lung cancer ranks first among cancer-related causes of death, with an estimated mortality rate of 18%. The global cancer burden is expected to increase by an estimated 47% (64-95% for developing countries and 32-56% for developed countries) in 2040 compared with 2020. However, this rate may worsen due to socioeconomic and demographic changes [2].

Histologically, there are two subtypes of lung cancer: small cell lung cancer (about 15% of cases) and non-small cell lung cancer (NSCLC, about 85% of cases) [3]. NSCLC is often diagnosed at advanced stages when metastases have already formed, contributing to a poor prognosis and a low overall survival rate [4]. The main lung cancer treatment modalities include chemotherapy, radiation, and/or surgery [5]. Platinum-based drugs are commonly used in first-line therapy to eradicate NSCLC [6]. However, this chemotherapy alone results in only modest improvement in patient survival. Similarly, a review of lung cancer treatment reported that platinum-based combination therapy with gemcitabine, paclitaxel, tyrosine kinase inhibitors, or angiogenesis inhibitors showed no limited or significant difference in overall survival [7]. In this way, the need for new agents and/or combined treatment strategies to improve efficacy, safety, and resistance issues in the treatment of lung cancer is emphasized. Nowadays, the beneficial effects of various bioactive phytochemicals in chemotherapy are the focus of interest, and studies on this topic are increasingly being conducted [8-11].

Berberine (BBR), long known and used in traditional medicine, could be a promising therapeutic option for lung cancer because it is an effective and safe anticancer phytochemical. BBR is a quaternary benzisoquinoline alkaloid that has been isolated from many medicinally important plants such as *Berberis vulgaris*, *Hydrastis canadensis*, and *Coptis chinensis* [12]. Over the years, research has shown that BBR has a wide range of therapeutic applications against a variety of diseases, including cancer. It has been suggested that BBR may exert therapeutic effects by regulating various molecular targets in different cancer cells, including gastric, colon, prostate, breast, and lung cancers [13-15]. Several studies have shown that BBR strongly suppress the proliferation, growth, and metastasis of NSCLC through various mechanisms, including cell cycle arrest, apoptosis, and triggering autophagy and cell death [7,16]. In addition, BBR is thought to interact directly with DNA, telomerase, topoisomerase I, p53, NF-kB, nucleic acids including MMPs and estrogen receptors, as well as a variety of genes and proteins [13]. It has also been shown to prevent the development of resistance to chemotherapy, tumor metastasis, and recurrence through various molecular mechanisms, including immunotherapy [17-19]. In the literature, in addition to the anticancer effect of BBR alone, its synergistic effect with chemotherapeutic agents has also been reported in various types of cancer [20-24]. Taken together, this strengthens the hypothesis that BBR can sensitize lung cancer cells to standard chemotherapeutic agents through different mechanisms.

Main Points;

- Non-small cell lung cancer (NSCLC) is a type of cancer that is usually diagnosed at advanced stages and has a poor prognosis and low survival rate.
- Platinum-based chemotherapy, which is the mainstay of treatment, offers limited benefit due to drug resistance and side effects.
- Berberine, which attracts attention for its potent anticancer activity, showed synergistic cytotoxic effect with cisplatin and induced apoptosis in A549 cells.
- Berberine could enhance treatment efficacy as part of chemotherapy in the treatment of NSCLC.

There appears to be a need for newer therapies to improve treatment outcomes in lung cancer. There is strong evidence that BBR, both alone and in combination with chemotherapy, can play an important role. However, few studies have been conducted on the effect of BBR in combination with CIS in lung cancer [25]. The current study examined the effects of BBR on the cytotoxicity of standard chemotherapeutic agents CIS and the effects of co-treatment on apoptosis markers in A549 lung cancer cells to contribute to studies aimed at increasing the efficacy of lung cancer treatment.

MATERIALS AND METHODS

Chemicals

CIS (10 mg/20 ml, 1.665 mM concentrated solution for intravenous infusion) was purchased commercially from Kocak Pharma (Tekirdag, Turkey). BBR was purchased from Cayman Chemical Co (Michigan, USA) and stored at a concentration of 40 mM in dimethyl sulfoxide (DMSO; from Merck Co, Darmstadt, Germany) as stock solution at -20°C. Working concentrations were freshly prepared by dilution with cell culture medium to a final concentration of DMSO ≤0.5%. Dulbecco's phosphate-buffered saline (PBS), glutamine, Dulbecco's Modified Eagle Medium (DMEM) with high glucose content, methylthiazolyldiphenyltetrazolium bromide (MTT), penicillin-streptomycin, and trypan blue were purchased from Sigma Aldrich Co (St. Louis, USA). Heat-inactivated fetal bovine serum (FBS) was purchased from Capricorn Scientific (Ebsdorfergrund, Germany) and trypsin-EDTA from Thermo Fisher Scientific Inc (Waltham, MA, USA). Human Bax and Cas3

Elisa kits from Bioassay Technology Laboratory (Birmingham, UK) were used for the experiments, and all analyzes were performed according to the manufacturer's protocols.

Cell Culture

A549 cells (human lung adenocarcinoma cell line) were provided by the American Type Culture Collection (ATCC; Rockville, MD, USA). Cells were maintained in DMEM cell culture medium. All media were supplemented with 10% FBS and 1% penicillin/streptomycin solution in a 95% humidified incubator with 5% CO_2 at 37 ◦C.

Cytotoxicity Test

The cytotoxic effect of the applied treatments on A549 cancer cells was determined using the MTT assay described by Mossmann [26]. Briefly, cells were plated at a density of 1×10^4 cells per well (counted with trypan blue) in 96-well plates. After 75% attachment, cells were first treated for 24 hours with various concentrations of CIS (1.95, 3.91, 7.81, 15.62, 31.25, 62.5, 125, or 250 μM) or BBR (3.91, 7.81, 15.62, 31.25, 62.5, 125, 250, 500, 1000, or 2000 μM) to determine their half-maximal inhibitory concentration (IC50). Control cells were incubated with 0.5% DMSO. After 24 hours, the cells were incubated with MTT solution (5 mg/mL in PBS) for 4 hours at 37°C in the dark. The medium was then discarded and 100 μL of dissolution solution (DMSO) for formazan crystals was added. The color changes were measured at 570 nm using a microplate reader (Epoch, Biotek, USA). IC50 values of CIS and BBR were calculated by nonlinear regression (curve fitting) of cytotoxicity data using the dose-response inhibition equation (log inhibitor vs normalized response variable slope) with GraphPad Prism 9.5.0 (GraphPad Software, San Diego, CA, USA).

Determination of Synergy

To determine the effects of the combined treatment of CIS and BBR, cells ($1x10^4$/well) were seeded in 96-well plates and incubated for 24 hours. The cells were then incubated again for 24 hours with different concentrations of CIS or BBR or combinations thereof (with different concentrations in non-constant ratios). Based on the MTT data, the combination indices (CIs) were defined according to the isobologram and median effect equality method developed by Chou and Talalay [27] using CompuSyn V1.0 software (ComboSyn, Inc.). According to this method, CI values below 1.0 indicate synergy and values above 1.0 indicate antagonism.

***Enzyme-linked* immunosorbent assay (Elisa) for the detection of apoptotic proteins**

Commercially available Elisa kits were used for the analysis of Bax and Cas3 levels in the supernatants. All steps were performed according to the manufacturer's instructions. OD values were analyzed using a microplate reader (at 450 nm). Using the standard concentrations, a graph was generated and used to calculate the protein concentrations of the samples. The protein concentrations of each treatment group were calculated as pg/mg protein.

Statistical Analysis

Quantitative data were expressed as mean ± standard deviation (n=3). Significant comparisons between groups were performed with ANOVA followed by post hoc comparisons with Tukey's HSD test. All statistical analyses were performed with GraphPad Prism 9.5.0. The statistical significance threshold was set at $p < 0.05$.

RESULTS

BBR inhibited proliferation of A549 lung cancer cells

The cytotoxic effect of BBR was investigated using the MTT assay on A549 lung cancer cells. Cells were treated with different concentrations of BBR (3.91-2000 μM) for 24 hours. The results showed that BBR inhibited cell viability and proliferation in a dose-dependent manner. The IC50 values of BBR were determined to be 131.90 μM for 24 hours (Table 1). In addition, the IC50 value of CIS (1.95-250 μM) was 7.21 μM for 24 hours (Table 1). The IC50 values were used in the next steps of our study.

Table 1. IC_{50} of BBR and CIS in A549 for 24 h

Groups	IC_{50} (μM)	95% Confidence Interval (Min-Max)	r^2
BBR	131.90	79.41-212.00	0.843
CIS	7.21	6.12-8.51	0.956

Abbreviation: CIS, Cisplatin; BBR, Berberin.

The combination of BBR and CIS has a strong synergistic effect on A549 cells

To investigate whether BBR has synergism with CIS on lung cancer cell viability, combination groups were formed based on IC50 values, which included lower and higher concentrations of IC50. Cells were grown with concentrations of BBR IC50x2, IC50, and IC50/2 (approximately 264, 132, and 66 μM) in combination with IC50 and IC50/2 concentrations of CIS

(approximately 7 and 3.5 µM, respectively). After 24 hours of incubation, absorbance values obtained by the MTT assay were entered into the CompuSyn program. CI values were calculated according to the Chou-Talalay method used for preliminary evaluation of combinations (Table 2). We found that the combination of BBR and CIS suppressed A549 cell growth more than monotherapy, and the CI value was less than 1.0 in all groups studied. On the basis of these data, we concluded that the combination of BBR and CIS had a strong cytotoxic effect at all concentrations studied. We found the lowest CI value (0.34±0.05), ie, the strongest synergism, in the group treated with both CIS and BBR at IC50 concentrations.

Table 2. The combination index (CI) values of combinations of BBR with CIS in A549 lung cancer cells.

Combinations	CI values
CIS (7 µM) + BBR (264 µM)	0.40 ±0.07
CIS (7 µM) + BBR (132 µM)	0.34 ±0.05
CIS (7 µM) + BBR (66 µM)	0.47 ±0.05
CIS (3.5 µM) + BBR (264 µM)	0.85 ±0.10
CIS (3.5 µM) + BBR (132 µM)	0.85 ±0.07
CIS (3.5 µM) + BBR (66 µM)	0.79 ±0.07

Abbreviation: CIS, Cisplatin; BBR, Berberine; CI, Combination index.

Co-treatment with BBR promoted CIS-induced apoptosis in A549 lung cancer cells

Commonly used markers for in vitro detection of apoptosis include the level of Bax, a pro-apoptotic protein, and the activity of Cas3, an effector caspase. To determine whether CIS +BBR co-treatment can induce apoptosis, A549 lung cancer cells were treated with IC50 concentrations of CIS or CIS +BBR for 24 hours, and Bax and Cas3 protein levels were measured by Elisa (Figure 1).

The amount of Bax protein, which plays an important role in regulating apoptosis, was calculated with means and standard deviations of 23.07 ± 0.79, 27.69 ± 1.06, 64.65 ± 4.28 pg/mg for the control, CIS, and CIS +BBR groups, respectively. Concurrent treatment of CIS with BBR significantly increased the amount of Bax protein compared to control and CIS ($p < 0.001$). The means and standard deviations of Cas3 protein levels were calculated as 61.70 ± 2.35, 100.54 ± 1.53, 180.52 ± 10.50 pg/mg for C, CIS and CIS +BBR groups, respectively. CIS co-treatment with BBR significantly increased Cas3 protein levels compared to control and CIS groups ($p < 0.001$). Taken together, these findings indicate that co-treatment shows synergism for apoptosis-inducing activity in A549 cells based on Bax and cas3 protein levels.

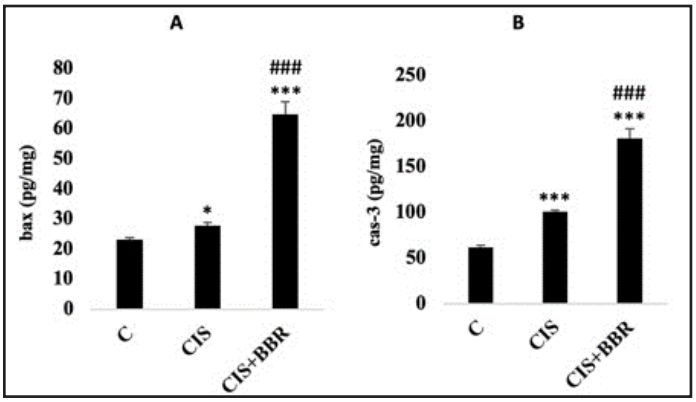

Figure 1. The effect of CIS alone or in combination with BBR on various proteins bax (A) and cas-3 (B) amounts associated with apoptosis in A549 lung cancer cells for 24 h. The results are represented mean ± standard deviation of three independent experiments. C: DMSO-treated (0.5%) control, CIS: Cisplatin (at IC_{50} doses), BBR: Berberine (at IC_{50} doses). (*compared to C $p < 0.05$; *** compared to C $p < 0.001$; #compared to CIS $p < 0.05$; ###compared to CIS $p < 0.001$).

DISCUSSION

Lung cancer is a major cause of morbidity and mortality [2]. Platinum-based chemotherapy, which is now a mainstay of treatment, offers limited benefit due to drug resistance and side effects [28]. Studies on combination therapies with various bioactive phytochemicals are increasingly being conducted to improve treatment efficacy [9,11]. BBR is a promising therapeutic option for lung cancer due to its potent and safe anticancer activity. BBR is known to exert antiproliferative effects on many human cancer cells through various molecular mechanisms [7,16]. However, the therapeutic efficacy of BBR in combination with platinum-based chemotherapy in lung cancer has not been adequately studied. Determining the molecular mechanism underlying the potential synergistic effect is critical for cancer treatment. In the present study, we researched the cytotoxic effects of CIS + BBR combination treatment in A549 cells and its potential effects on apoptotic signalling pathways.

In our study, the cytotoxic effect of BBR and CIS on A549 cells was first evaluated by a 24-hour MTT assay, and the IC50 values were 131.9 µM and 7.2 µM, respectively. The results demostrated that both BBR and CIS suppressed cell proliferation in cells in a concentration-dependent manner.

Consistent with our results, several studies have revealed that BBR can have an antiproliferative effect on lung cancer cells [24,29,30]. Kumar et al. reported that BBR decreased the viability of A549 cells (66.38%) even at the lowest concentration tested (3.125 μM), and the viability of cells treated with 50 μM BBR was 49% during 48 h incubation by MTT assay [29]. IC50 values of 24.5 and 21.0 μg/ml for 72 hours of incubation were obtained for NSCLC cells H460 and H1975, respectively [24]. A current study reported that cell death was significantly induced in A549 and PC9 lung cancer cells treated with BBR (0-160 μM) in a concentration- and time-dependent manner. IC50 values of 80-100 μM were also reported using the CCK8 assay for 48 hours [31]. It was noted that the calculated IC50 values vary in the literature. It is clear that the cytotoxic profiles may vary depending on the different assays applied and the cell lines used.

Furthermore, we investigated the synergistic cytotoxic effects in A549 cells at different concentrations of the combination groups based on the IC50 values. According to the MTT data, the CI value was less than 1 in all studied groups, indicating synergism. These results indicate that BBR can sensitize CIS cytotoxicity in A549 cells. The lowest CI value, i.e., the strongest synergism, was obtained in the combination group at the IC50 concentrations of both CIS and BBR. Therefore, we used IC50 values in the molecular mechanism experiments. It has been reported in the literature that BBR as part of the combination can show synergistic effects in various cancer chemotherapies in humans. In a study supporting our findings, a potential synergistic effect of BBR (at non-cytotoxic doses, 0-10 μM) with CIS was demonstrated by significantly reducing the colony-forming potential of A549 lung cancer cells [23]. In addition, BBR was reported to increase doxorubicin (DOX)-mediated resistance and sensitize lung cancer cells to DOX. The molecular data from this study showed that BBR can suppress the activation of *Signal Transducer and Activator of Transcription* 3 (STAT3, a protein that plays a critical role in malignant transformation and progression), preventing cell proliferation and inducing apoptosis in DOX-resistant lung cancer cells (H460 and H1975) [24]. A recent study has shown that the combined treatment of BBR with osimertinib (inhibitor of *epidermal growth factor receptor* (EGFR) tyrosine kinase) has a synergistic anticancer effect on lung cancer cells and may act as a gene (*MET*) inhibitor related to the resistance mechanism [11]. Some studies have shown that BBR in combination with melatonin [31], cinnamaldehyde [32], and icotibinib [33] has the potential to exert anticancer effects by targeting several genes and/or signaling pathways that play important roles in lung cancer cell growth, invasion, and metastasis. Besides the chemo-cytotoxic potential of BBR, the potential for radiosensitization has also been reported in NSCLC [34].

Besides lung cancer, a very recent study reported that BBR induced synergistic cell growth inhibition in human epidermoid carcinoma cells (A431) with Erlotinib -inhibitor of EGFR tyrosine kinase- using tumor xenograft models *in vitro* and *in vivo*. This anticancer effect was associated with greater inhibition of pAKT and pEGFR, as well as inhibition of Bcl-2 and cyclin D expression. This study supports the combination of BBR with erlotinib as a novel strategy for the treatment of patients with EGFR-positive tumors [20]. BBR induces ionizing radiation mediated cytotoxicity associated with cell cycle arrest in G2/M phase and autophagic cell death. In the *Lewis* lung carcinoma mouse model, synergistic treatment of BBR (1 and 2 mg/kg) with ionizing radiation resulted in a reduction in tumor volume (approximately 48% and 22%, respectively) [34]. In addition, randomized trials in patients with NSCLC treated with radiotherapy showed that BBR therapy (20 mg/kg once daily for 6 weeks) improved baseline lung function and dramatically decreased the incidence of radiation-induced lung injury. The expression of soluble intercellular adhesion molecule-1 and transforming growth factor-beta-1, which are included in the pathogenesis of radiation-induced inflammation, was also reduced by this combination therapy [35]. Taken together, these studies support the investigation of the potential of BBR as an adjuvant in lung cancer. The findings propose that BBR may have a synergistic effect with platinum-based therapy, but the molecular mechanism underlying this synergistic effect has not been fully clarified.

In various *in vitro* and *in vivo* lung cancer models, BBR has been shown to contribute to both apoptosis and autophagy in lung cancer cells by upregulating the expression of apoptotic and/or pro-apoptotic signaling pathways/proteins and targeting AMPK/mTOR/ULK1 signaling pathways [30,36,37]. Apoptosis induction is thought to be an important pathway for the synergistic anticancer effects that occur with bioactive phytochemicals in chemotherapy [7,16]. In our study, we demonstrated that CIS +BBR co-treatment effectively inhibited A549 cell proliferation through in vitro induced apoptosis. Analysis of known apoptotic proteins revealed that they can induce cellular apoptosis. We found that this co-treatment increased the level of Bax protein, which promotes apoptosis, compared to control and CIS ($p < 0.001$).

Increased Bax levels generally lead to enhanced mitochondrial membrane permeability and the release of proapoptotic factors such as cytochrome c from mitochondria into the cytosol, which initiates the activation of the caspase cascade and promotes the progression of apoptosis [38]. In support of our findings, our study also analyzed higher Cas-3 protein levels compared to the control and CIS groups ($p < 0.001$). In a study consistent with our results, BBR was reported to inhibit proliferation of NSCLC cells (A549 and PC9), promote apoptosis, and suppress metastasis via the MMP-2, Bcl-2/Bax, and Jak2/VEGF/NF-Kb/ AP -1 signaling pathways [36]. Another study recently reported that it strongly suppressed ROS -mediated ASK1/JNK activation, Cas3 cleavage, cytochrome c release, mitochondrial membrane depolarization, and dose- and time-dependent cell growth in NSCLC cell lines (A549 and PC9) treated with BBR (40, 80, 120 μg/mL). The study data correlated with nude mouse xenograft tumor experiments [30]. Ni et al [39] reported that BBR decreased the proliferation of NSCLC cells and suppressed colony formation in vitro, and inhibited the growth of NSCLC tumors in lung tumor models, resulting in prolonged survival. They also reported that BBR suppressed the growth of NSCLC cells by suppressing DNA repair and replication [39]. Overall, the therapeutic effects of BBR on cancer cells and the induction of apoptosis seem to be a promising combination candidate for chemotherapy of NSCLC patients.

Despite its potent anticancer potential, BBR is subject to several distinct limitations that restrict its clinical use. An example of these limitations is a study that showed that BBR alone or in combination with 5 FU reduced the growth of lung cancer stem cells (H460) but increased the survival of cells in the secondary population [40]. This study requires further investigation before BBR can be incorporated into clinical therapy. One of the main disadvantages of BBR is its low bioavailability. Therefore, high doses are required to achieve therapeutic goals. Many studies have attempted to develop approaches such as the use of absorption enhancers or co-solvents, salt formation, modification of the structure of BBR, and/or nano-based delivery systems to overcome this problem and increase therapeutic efficacy [12,22,41]. For example, a study on breast cancer cells (4T1) reported that the nanodrug design consisting of DOX and BBR effectively inhibited tumor growth and also significantly suppressed lung metastasis by blocking the HMGB1-TLR4 axis. This nanodrug design study indicates that it will shed light on the development of biomimetic nanodrugs for effective and safe chemotherapy [22]. Optimization of these approaches and development of an effective strategy for combined use in chemotherapy may be critical for the treatment of lung cancer.

Our results show that BBR can sensitize CIS cytotoxicity in A549 cells and has a synergistic anti-cancer effect by inducing apoptosis together with CIS. Considering the low bioavailability of BBR, which limits its therapeutic use, technological approaches with higher bioavailability of BBR should be investigated in research studies to address this issue. We are aware of the limitations of our study. In addition to studying cytotoxicity and the apoptotic process, other techniques can be used to investigate various possible cellular pathways such as cell cycle checkpoints, antioxidant defense system, genotoxicity, and inflammation. Our results showing the complementary role of BBR in enhancing the therapeutic efficacy of CIS in the treatment of lung cancer provide promising new data for the relevant literature. This study may pave the way for in vivo and clinical research to develop therapeutic strategies for lung cancer.

CONCLUSION

It has been shown that BBR at an IC50 concentration can enhance the anticancer effect of CIS by inducing caspase-dependent apoptosis in lung cancer cells. BBR may play an important role in increasing treatment efficacy, reducing side effects, and lowering treatment costs, alone or as part of chemotherapy in various human cancers. The existing data still need to be supported by *in vivo* and clinical studies. Considering the low bioavailability of BBR, various treatment strategies can be developed by formulating nanotechnology-based systems to address this issue.

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Original Research

Kinesiophobia, Dyspnea, Pain, Fatigue, Depression, Anxiety, Stress, and Balance in Adolescent Volleyball Players Who Have Had COVID-19

Elif Şahin[1], Gülşah Bargı[2]

[1] Izmir Democracy University, Institute of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey
[2] Izmir Democracy University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey

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Correspondence
Gülşah Bargı
Address: Mehmet Ali Akman Quarter, 13th street, No. 2, 35140 Güzelyalı, Konak, İzmir, Turkey
E-mail: gulsahbargi35@gmail.com

ABSTRACT

Objective: It is still unclear to what extent kinesiophobia, dyspnea, pain, fatigue, mood, and balance are affected in adolescent volleyball players who have had COVID-19. Therefore, present study aimed to comparatively investigate kinesiophobia, dyspnea, pain, fatigue, depression, anxiety, stress, and balance between adolescent volleyball players with and without post-COVID-19.

Methods: Adolescent volleyball players between ages of 10-19 (n=40) were included in the study between May 2022 and August 2022 and divided into those who have had COVID-19 (n=18) and those who have never had COVID-19 (n=22). Measurements of kinesiophobia (Tampa Scale of Kinesiophobia), dyspnea perception in daily living activities (Modified Medical Research Council Dyspnea Scale), severity of pain and fatigue (Numerical Rating Scale), depression, anxiety, and stress levels (Short Form of Depression Anxiety Stress Scale), static balance (balance test on one leg), and dynamic balance (standing functional reach test) were performed in all volleyball players at once.

Results: There was no statistically significant difference between groups in demographic characteristics, kinesiophobia, dyspnea, pain, fatigue, depression, stress, and balance values ($p>0.05$). However, anxiety scores of adolescent volleyball players who have not had COVID-19 were statistically significantly higher than those of adolescent volleyball players who have experienced COVID-19 ($p<0.05$). The incidences of anxiety (n=5, 27.8% versus n=11, 50%) were similar between groups ($p>0.05$).

Conclusions: During the prolonged COVID-19 pandemic period, kinesiophobia, dyspnea, pain and fatigue perceptions, depression, stress, and balance levels were found to be similar in adolescent volleyball players regardless of their post-COVID-19 status. However, anxiety is more common in adolescent volleyball players without post-COVID-19. Therefore, underlying causes of anxiety observed in adolescent volleyball players without post-COVID-19 should be investigated.

Keywords: Adolescent Volleyball Players, COVID-19, Balance, Depression, Kinesiophobia

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been experienced as a deadly respiratory pandemic in the past years and has adversely changed both the style of sports competition and physical condition of athletes. Face-to-face participation in sports organizations has been cancelled and/or postponed during the pandemic [1]. While the anxiety level of elite athletes increased during social isolation and quarantine periods, it

decreased during the return to a controlled social life. During the restrictions period, while the workout times of young athletes decreased, the time spent outside, and duration of sleep increased. By 86% of these young athletes were able to continue their training program by maintaining social distance during this period. Older athletes had higher rates of depression while younger female athletes had higher levels of anxiety. By 10% of young athletes and 20% of young people changed their sports-related goals during the pandemic process [1].

Due to the rapid transmission feature of COVID-19, mandatory restrictions and strict quarantine rules have been applied in all parts of the society for a long time all over the world. For this reason, the incidences of kinesiophobia defined as the fear of moving, anxiety, depression, and stress, have increased in both individuals with post-COVID-19 and without post-COVID-19 [2-5]. Although children have been less affected by the COVID-19 pandemic than adults, depressive symptoms and anxiety have also been observed in children and adolescents during this period [6,7]. Besides anxiety and depression [5], dyspnea and fatigue are also among the symptoms that can be seen in individuals afflicted with COVID-19 [3,8]. Unfortunately, individuals with post-COVID-19 may continue to experience some symptoms such as dyspnea, pain, and fatigue even months after the infection [3,9]. As previously shown, low back and neck pain have been also observed in mild-COVID-19 patients in home quarantine during the isolation period and post-COVID-19 period [10]. It has been reported that physical performance including balance ability decreases in elderly individuals who have had COVID-19 [8,11]. However, studies evaluating static or dynamic balance in adolescents with post-COVID-19 have not been found in the literature.

As far as we know, it is not yet known to what extent kinesiophobia, dyspnea, pain, fatigue, depression, anxiety, stress, and balance are affected in adolescent volleyball players who have had COVID-19 compared to their peers who have never had COVID-19. For this reason, in this study, it was aimed to reveal the effects of COVID-19 on these outcome values in adolescent volleyball players and to test the hypotheses by comparing kinesiophobia, dyspnea, pain, fatigue, depression, anxiety, stress and balance between adolescent volleyball players without post-COVID-19 and with post-COVID-19.

Main Points;

- During the prolonged COVID-19 pandemic, higher anxiety scores were evident in adolescent volleyball players without post-COVID-19.
- When compared to the scores of kinesiophobia, dyspnea in activities of daily living, pain, fatigue, depression, stress, static balance and dynamic balance scores, there were no differences between volleyball players with and without post-COVID-19.
- Kinesiophobia, dyspnea, pain, fatigue, depression, stress, static balance and dynamic balance disorders existed at similar rates in adolescent volleyball players regardless of having post-COVID-19.
- It is important to evaluate adolescent volleyball players with multidisciplinary approaches when it comes to situations that affect public health in every way, such as COVID-19 pandemic.

MATERIALS AND METHODS

Study Design

Ethics committee approval of this cross-sectional study was obtained from Izmir Democracy University Non-Interventional Clinical Research Ethics Committee on 2022-04-06 with the decision number 2022/04-10. Necessary permissions for the study were received from the Ministry of Health and the Ministry of Youth and Sports. Signed consent forms were taken from all volleyball players and their parents who were informed about the study. In this cross-sectional study, demographic and descriptive knowledge about the volleyball players were recorded. The measurement parameters are kinesiophobia, dyspnea, pain, fatigue, depression, anxiety, stress, and balance levels that were completed in each volleyball player in approximately 30 minutes in one day.

Study Population

Adolescent volleyball players were included in the study between May 2022 and August 2022. They were athletes who actively participated in the tournaments held in Isparta province under the Ministry of Youth and Sports. Inclusion criteria for the players who have had COVID-19 were i) being between the ages of 10-19 (adolescent/adolescence), ii) volunteering to participate in the study, iii) being able to understand and answer the questionnaires and scales applied within the scope of the study, iv) diagnosis of post-COVID-19 (having a positive result of polymerase chain reaction test or having a chest X-ray or lung tomography result consistent with COVID-19 infection despite a negative result of polymerase chain reaction test) and v) having discharged from hospital due to COVID-19 and/or recovered in quarantine at home. Exclusion criteria for the players who have had COVID-19 were i) having any physical or mental disability/disease and/or cognitive impairment that

could prevent the evaluations, ii) having any acute infection and/or health problems, iii) being newly diagnosed with COVID-19 and therefore in quarantine at home or receiving treatment in hospital and/or iv) having suspected COVID-19.

Inclusion criteria for the players who have not had COVID-19 were i) being between the ages of 10-19 (adolescent/adolescence), ii) volunteering to participate in the study and iii) being able to understand and answer the questionnaires and scales applied within the scope of the study. Exclusion criteria for the players who have not had COVID-19 were i) having any physical/mental and/or cognitive impairments that could prevent the evaluations, ii) having any acute or chronic infection and/or health problems, iii) having had COVID-19 and/or iv) having suspected COVID-19.

Measurements

Kinesiophobia

The Tampa Scale of Kinesiophobia was used to evaluate kinesiophobia status of adolescent volleyball players [12]. Turkish version of this scale is valid and reliable which consists of 17 items in total. Each item is scored in a four-point Likert type as "strongly disagree (1 point), disagree (2 points), agree (3 points) and totally agree (4 points) [13]. The scoring of the 4th, 8th, 12th, and 16th items is calculated by reversing. The total score is calculated by summing up the corresponding score for the answers from all items. The lowest total score that can be obtained from the scale is 17 and the highest total score is 68. A high score from the scale indicates an increase in kinesiophobia status of the individual. A cut-off score above 37 points is defined as a high degree of kinesiophobia [12]. The volleyball players answered this scale themselves.

Dyspnea

Dyspnea is a complex subjective sensation that is an important feature of cardiac and/or pulmonary system diseases [14]. The severity of dyspnea and dyspnea occurring during activities of daily living in adolescent volleyball players were questioned using the Modified Medical Research Council Dyspnea Scale [14]. This dyspnea scale consists of five levels based on various physical activities causing dyspnea. These levels are scored from 0 to 4. The first level indicates the absence of dyspnea (0 point), and the last level indicates severe shortness of breath felt even during dressing and undressing activities (4 points). As the score obtained from the scale increases, the perception of dyspnea during activities of daily living also increases [14].

Pain and Fatigue

The severity of pain and fatigue at rest and during activities of daily living was evaluated using the Numerical Rating Scale which is a verbal, one-dimensional, easy-to-use, and simple scale [15,16]. This scale expresses the severity of pain and fatigue with integers from 0 (no pain/fatigue) to 10 (the worst possible pain/fatigue). This scale, which provides a single-item measurement, has horizontal and vertical forms [15,16]. Volleyball players participating in the study made markings on the vertical form.

Depression, Anxiety, and Stress

The Short Form of Depression Anxiety Stress Scale was used to evaluate the mood of adolescent volleyball players [17]. This form consists of 21 items. There are seven items for each of the sub-assessments of depression, anxiety, and stress [17]. Each item is suitable for 4-point Likert-type scoring and is scored between 0 and 3. Responses to each item are "not suitable for me (0 point), slightly suitable for me (1 point), usually suitable for me (2 points), and completely suitable for me (3 points)" [17]. If a total of 5 points or more is obtained from the depression sub-assessment, a total of 4 points or more from the anxiety sub-assessment, and/or a total of 8 points or more from the stress sub-assessment, it is stated that the individual has the related problem. Turkish version of this form is valid and reliable [18].

Static and Dynamic Balance

The balance test on one-leg is a simple field test which is used to measure the static aspects of balance [19]. This test is commonly used to assess static balance ability in children. It has been reported that children older than 10 years of age can maintain the balance test on one-leg between 53 and 104 seconds [20]. This test was performed separately for the right and left lower extremities of adolescent volleyball players on one-leg on a hard floor. The test was performed with both eyes open and closed. Volleyball players stood with their hands on their waists before the test. When they were ready, they started to stand on one leg (another knee in 90° flexion), keeping their balance on one leg, looking ahead and not touching the other legs. As soon as the volleyball players lifted their feet from the ground, the time began. The maximum time to stand on one leg was recorded in seconds with a stopwatch separately for the right and left sides and for the tests with eyes open and closed. The test was stopped when the volleyball player broke the fixed position or lowered the raised foot. Volleyball players had two attempts for each test. The measurement values obtained by staying in the best and correct position were recorded [19].

The standing functional reach test was used to assess functional/dynamic balance performance of the volleyball players. The use of this test is appropriate in the evaluation of balance in children population. A normal value range is reported as 23-36.5 cm in children aged between 6-12 in the Turkish population [21]. Adolescent volleyball players were asked to stand side by side without touching the wall while the standing functional reach test was being applied. Then, they were asked to extend their arms at the side of the wall in 90° flexion, elbow extension and parallel to the wall. The distance value between the starting point and the farthest point reached was measured and recorded in centimeters. This measurement was repeated three times, performed separately from the right and left sides. The three values obtained for each side were averaged [22].

Statistical Analyses

The sample size was calculated using the program GPower (G*Power 3.0.10 system, Franz Faul, Universität Kiel, Germany). To detect the difference in kinesiophobia scores (9.1) between two independent groups for a statistically significant level by reaching an α value of 0.05, an effect size of 1.5, and a power of 95%, at least 18 players for post-COVID-19 group and at least 10 players for non-post-COVID-19 group were calculated [23]. At the end of the study, statistical analyzes were performed using Windows-based Statistical Program for Social Sciences version 15.0. Descriptive analyzes were presented using frequency (n), percent (%), median, interquartile range (IQR), mean and standard deviation (x±SD) values. Independent Sample t-test was used to compare the variables with normal distribution, Mann-Whitney U test was used to compare variables that did not fit the normal distribution, and the Chi-square test was used to compare the categorical variables. While the differences between the groups of the normally distributed variables were given as the difference between the means (mean difference) and the lower and upper limits of the 95% confidence interval (95%CI), the differences between the groups of the non-normally distributed variables were given as the U value. The probability of error in statistical analysis was accepted as $p<0.05$.

RESULTS

The study included 43 adolescent volleyball players who actively participated in tournaments, 19 of whom had COVID-19 and 24 had not. One of the volleyball players who have had COVID-19 and two of the volleyball players who have not had COVID-19 were excluded from the study because they were suspected of being COVID-19 positive. The study was completed with 18 post-COVID-19 and 22 non-post-COVID-19 volleyball players. All volleyball players with post-COVID-19 have completed their COVID-19 treatment in quarantine at home and these athletes were volleyball players who have had mild COVID-19. When the descriptive and physical characteristics of the volleyball players were compared between the groups, no statistically significant differences were found (Table 1, $p>0.05$).

No statistically significant difference was found between the groups when the kinesiophobia, dyspnea, pain and fatigue felt at rest and during activities, depression, stress, static and dynamic balance scores of the volleyball players were compared (Table 2-3, $p>0.05$). The anxiety scores of volleyball players without post-COVID-19 were statistically significantly higher than those who had experienced COVID-19 (Table 2, $p<0.05$). No statistically significant differences were found in the rates of high degree of kinesiophobia, dyspnea, pain, and fatigue at rest and during activities, depression, anxiety, and stress (Table 1, Figure 1, $p>0.05$). One (5.6%) of the volleyball players with post-COVID-19 and 2 (9.1%) who have not had COVID-19 had dyspnea while walking fast on a flat road or climbing a slight slope ($p>0.05$).

Table 1. Distribution of descriptive and physical characteristics of volleyball players

	Volleyball players with post-COVID-19	Volleyball players without post-COVID-19	p value
	x±SD / Median (IQR)	x±SD / Median (IQR)	
Age (year)	14.72±2.72	14.27±3.06	0.630
Height (cm)	166.67±8.96	160.73±9.76	0.054
Weight (kg)	56.67±11.45	51.09±8.85	0.090
Body mass index (kg/m^2)	20.2±2.75	19.64±2.01	0.458
Year of volleyball playing	1.5 (3.25)	2 (2.25)	0.867
	n; %	n; %	
Gender (female/male)	11; 61.1% / 7; 38.9%	18; 81.8% / 4; 18.2%	0.173
Chronic illness	2; 11.2%	2; 9.1%	0.499

High degree of kinesiophobia	8; 44.4%	6; 27.3%	0.257
Pain at rest	3; 16.7%	7; 31.8%	0.464
Pain during activities	6; 33.3%	10; 45.5%	0.436
Fatigue at rest	6; 33.3%	9; 40.9%	0.622
Fatigue during activities	8; 44.4%	9; 40.9%	0.822
Depression	5; 27.8%	7; 31.8%	0.781
Anxiety	5; 27.8%	11; 50%	0.154
Stress	4; 22.2%	6; 27.3%	0.714

n: frequency, %: percent, cm: centimeters, kg: kilograms, x: mean, SD: standard deviation, IQR: interquartile range, Mann-Whitney U test *p<0.05, Chi-square test ** p<0.05, Independent Sample t-test ***p<0.05.

Table 2. Comparison of kinesiophobia, dyspnea, pain, fatigue, depression, anxiety, and stress scores in volleyball players

	Volleyball players with post-COVID-19	**Volleyball players without post-COVID-19**		
	Median (IQR)	**Median (IQR)**	**U value**	**p value**
Kinesiophobia score (17-68)	33.5 (12.75)	35 (8)	189	0.806
Dyspnea score (0-4)	0 (0)	0 (0)	189	0.677
Pain score at rest (0-10)	0 (0)	0 (2)	167	0.267
Pain score during activities (0-10)	0 (2)	0 (2.25)	174.5	0.470
Fatigue score at rest (0-10)	0 (2.5)	0 (4)	183.5	0.650
Fatigue score during activities (0-10)	0 (2.5)	0 (1.25)	173.5	0.458
Depression score (0-21)	2.5 (5)	3 (4.25)	173.5	0.496
Anxiety score (0-21)	2.5 (3)	3.5 (4.5)	126	**0.047***
Stress score (0-21)	3.5 (5.75)	4.5 (5.25)	155	0.240
DASS total score (0-63)	6.5 (14.25)	11 (12.25)	135.5	0.089

DASS: Short Form of Depression Anxiety Stress Scale, IQR: interquartile range, Mann-Whitney U test *p<0.05.

Table 3. Comparison of static and dynamic balance scores in volleyball players

	Volleyball players with post-COVID-19 x±SD / Median (IQR)	**Volleyball players without post-COVID-19** x±SD / Median (IQR)	**Mean difference (95%CI) / U value**	**p value**
Evaluation of static balance				
Balance test on left one-leg with eyes open (sec)	62 (126.25)	48.5 (104.5)	166.5	0.392
Balance test on right one-leg with eyes open (sec)	60 (57.75)	78.5 (140.5)	163.5	0.348
Balance test on left one-leg with eyes closed (sec)	35 (18.75)	30 (26.5)	169	0.428
Balance test on right one-leg with eyes closed (sec)	33.5 (25)	36 (20)	192.5	0.881
Evaluation of dynamic balance				
Functional reach test (left, cm)	47.39±8.21	45.55±6.76	1.85 [(-2.94)-(6.63)]	0.440
Functional reach test (right, cm)	49 (13.83)	43.33 (12.63)	150	0.192

sec: second, cm: centimeters, x: mean, SD: standard deviation, IQR: interquartile range, 95CI%: 95% confidence interval, Mann-Whitney U test *p<0.05, Independent Sample t-test **p<0.05.

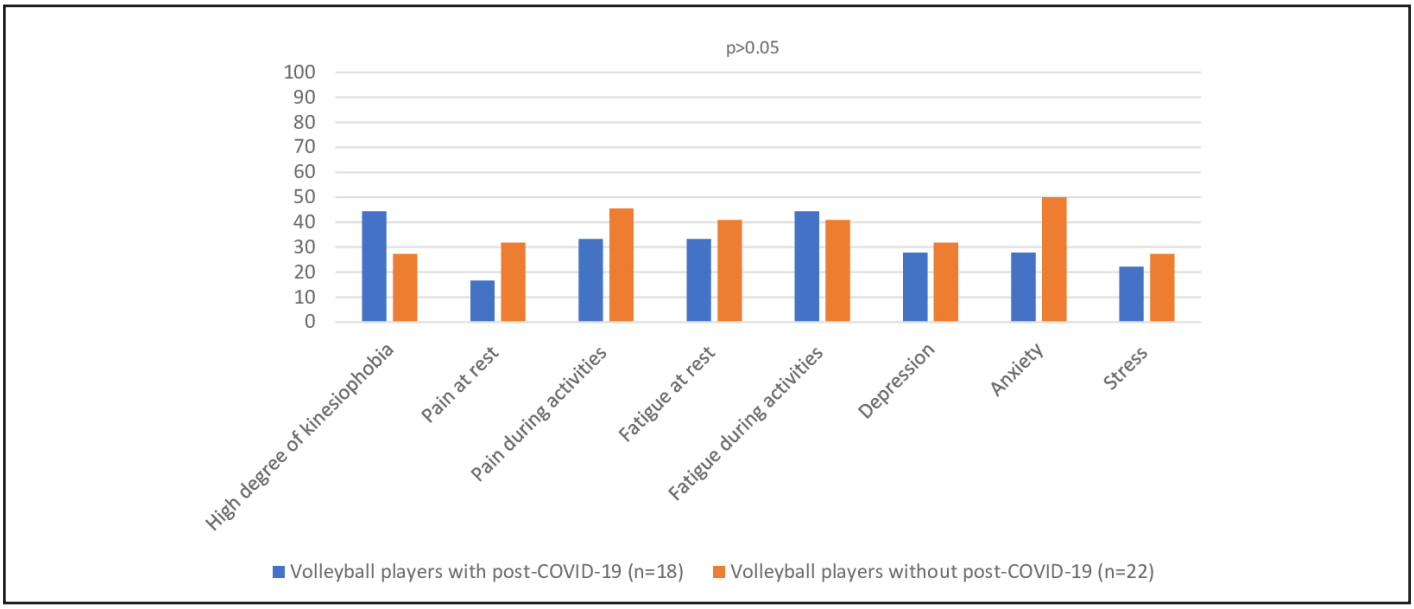

Figure 1. Comparison of high degree of kinesiophobia, pain, fatigue, depression, anxiety, and stress rates in volleyball players.

DISCUSSION

The most notable important findings of current study, which was firstly carried out on adolescent volleyball players with or without post-COVID-19 during the prolonged COVID-19 pandemic, to our knowledge, are as follows: i) The adolescent volleyball players without post-COVID-19 had higher anxiety scores, ii) Kinesiophobia, dyspnea in activities of daily living, pain, fatigue, depression, stress, static balance and dynamic balance scores were indicated to be similar in volleyball players with and without post-COVID-19, iii) High degree of kinesiophobia, feeling of pain at rest, feeling of pain during activities, feeling of fatigue at rest, feeling of fatigue during activities, depression, anxiety, and stress existed in some volleyball players with post-COVID-19, iv) High degree of kinesiophobia, feeling of pain at rest, feeling of pain during activities, feeling of fatigue at rest, feeling of fatigue during activities, depression, anxiety, and stress existed in some volleyball players without post-COVID-19.

In the COVID-19 pandemic, the incidences of physical inactivity and kinesiophobia, defined as the fear of movement, have increased in individuals due to mandatory restrictions and quarantine rules [2-4]. It has been found that the kinesiophobia scores were similarly higher in elderly individuals with and without COVID-19 [2]. Consistent with the results of this study, although high levels of kinesiophobia were reported in some of the adolescent volleyball players with and without post-COVID-19 in our study, kinesiophobia scores were similar between our groups. The kinesiophobia scores were found to be higher in adult individuals with post-COVID-19 compared to healthy adults who were evaluated in the second year of the pandemic [3,4]. Contrary to the results of these studies, in our study, no difference was found in terms of kinesiophobia scores in adolescent volleyball players with and without post-COVID-19. This difference observed in the kinesiophobia results of these studies may be due to the fact that the times when the measurements were taken in the studies coincided with the processes in which the pandemic passed with different intensities. Our study has been carried out more recently, the restrictions have been relaxed and unmasked socialization has been started during the evaluation period of the volleyball players. In addition, at that time, adolescents were rapidly adapting to face-to-face education. For this reason, the kinesiophobia score may have been found to be lower in the volleyball players in our study compared to the studies. Although the devastating effects of the COVID-19 pandemic on human health have decreased today, it should be considered that effects of the pandemic continue. Multidisciplinary approaches should be planned to improve these public health problems that may remain after the virus has passed in individuals with post-COVID-19.

Dyspnea is among the symptoms that can be seen in individuals with COVID-19 [3,8]. Elderly individuals with post-COVID-19, who were discharged after receiving acute care treatment for COVID-19 in the hospital and followed up in the outpatient service, had mild to moderate severity of dyspnea [8]. Another

study demonstrated that dyspnea score was found to be higher in individuals with post-COVID-19 compared to healthy individuals [3]. Although the difference in dyspnea scores between our groups has not been shown in our study, 5.6% of volleyball players with post-COVID-19 and 9.1% of volleyball players without post-COVID-19 had mild severity of dyspnea in activities of daily living. The fact that dyspnea was less common in adolescent volleyball players with post-COVID-19 compared to older adults who have experienced COVID-19 can be attributed to the higher incidence of comorbidities observed in elderly individuals. As seen, COVID-19 affects children less than adults and may show an asymptomatic course in children [24].

Fatigue (98%) and pain (87%) can be observed as long-term symptoms of COVID-19 [9]. Mild to moderate fatigue existed in elderly adults with post-COVID-19 [8]. It was also reported that pain and fatigue scores of individuals with post-COVID-19 were higher than the scores of healthy individuals [3]. In another study conducted in individuals with mild-COVID-19 showed that while neck pain was observed in these individuals in the pre-COVID-19 period (20%), during the isolation period of COVID-19 (35.6%) and in the post-COVID-19 period (13.3%), low back pain observed in these individuals in the pre-COVID-19 period (22.2%), during the isolation period of COVID-19 (42.2%) and in the post-COVID-19 period (13.3%) [10]. Consistent with these studies, adolescent volleyball players with and without post-COVID-19 had pain and fatigue both at rest and during activities in current study. Due to the severe impact of the SARS-CoV-2 virus at the onset of the COVID-19 pandemic, individuals with COVID-19 had higher rates of pain and fatigue, but these rates and scores decreased in individuals with post-COVID-19 as shown in current study. In fact, as seen in our study, the pain perceptions of individuals with post-COVID-19 were similar to healthy controls. However, considering relatively high rates of pain and fatigue observed in our healthy controls it can be said that the perception of pain and fatigue may have increased due to problems such as kinesiophobia, physical inactivity and fear of COVID-19.

Depressive symptoms and anxiety have been reported in children and adolescents during the pandemic period [6,7]. Our study proved that while volleyball players in both groups had similar rates of depression, stress, and anxiety (27.8% versus 50%), anxiety scores of the players without post-COVID-19 (median score (IQR): 3.5 (4.5)) were higher than others (median score (IQR): 2.5 (3)). Contrary to this result of our study, it has been reported that the depression scores of the young adult athletes who have had COVID-19 were higher than those who have not had COVID-19 while anxiety scores were similar between groups [25]. Moreover, Yıldız and Algün Doğu (2022) showed that the anxiety scores of female young adult athletes were higher than males [25]. The difference between these results may be due to the inclusion of young adult athletes with at least 5 years of licensed athlete history. As a matter of fact, it has been also reported that older athletes had higher depression scores in the COVID-19 pandemic [1]. Öksüz Çapanoğlu found the rate of anxiety to be higher in individuals who have had COVID-19 compared to individuals who have not had COVID-19, contrary to the results we found in our study [3]. On the other hand, no difference was observed in terms of anxiety and depression scores between these individuals [3]. It was also shown in the study published by Bargı in 2022 that the anxiety score may be higher in adults who have had COVID-19 compared to adults who have not had COVID-19 [4]. Adult individuals with and without post-COVID-19 were included in this newly published study, and the measurements were taken from these individuals in November 2021 and December 2021 [4]. As a result, it was found that anxiety (55.2% vs. 20%) and stress (34.5% vs. 5%) were observed more frequently in individuals with post-COVID-19, and anxiety scores were higher in individuals with post-COVID-19 compared to others [4]. Similarly, a study published by Tanrıverdi et al (2022) showed that 33.3% of adult individuals who have had mild or moderate COVID-19 had anxiety and 29.2% had depression [5]. As seen, the studies have demonstrated that individuals with post-COVID-19 had mood disorders including anxiety, stress, and/or depression [3-5]. In the literature, the incidences of depression, anxiety and stress in adults who have had COVID-19 are like the rates observed in our adolescent volleyball players with post-COVID-19. However, in our study, it is an advantage to have a healthy control group without post-COVID-19, whose the anxiety score was found to be higher. This may have been caused by the inclusion of adolescent volleyball players, who can be affected by the physical health status, emotions, and thoughts of other individuals (parents etc.) around them with COVID-19 [26]. In the study of Eroğlu and Yakşi, it was also stated that the anxiety score increased to the highest level in children who had both parents infected with COVID-19 [26]. On the other hand, the thought that having COVID-19 may adversely affect sports performance in athletes may have caused more anxiety in adolescent athletes who have not had COVID-19. As a

matter of fact, being psychologically weak both poses a risk for the physical and mental health of the athlete and reduces the quality of professional sports performance [25]. For this reason, considering the negative long-term effects of the COVID-19 pandemic on the mood of both children and adults with or without post-COVID-19, it is recommended to include these individuals in psychological counseling programs.

The results of present study regarding static and dynamic balance scores were similar in adolescent volleyball players with and without post-COVID-19 which is the firstly exposed in our study, to our knowledge. Similar to our results, balance scores of the individuals with post-COVID-19 were not different from controls [3]. On the other hand, it has been shown that physical performance, including balance, decreased in elderly individuals who have had COVID-19 [8,11]. It is an expected situation since balance disorders can be often seen in elderly people due to chronic comorbid diseases or as a part of the aging process [27]. However, it is reported that these problems can develop in the early stages of life in young people due to sedentary lifestyle. A study conducted in adult males demonstrated that the balance scores of physically active individuals are better than those of sedentary individuals [28]. In our study, due to the young age of the adolescent volleyball players engaged in active sports, balance problems may not have been detected. For this reason, the presence of balance problems in older individuals who have had COVID-19 should be investigated with appropriate evaluation methods.

The most important limitation of our study is that the star balance test, which allows the balance measurement to be used as a more differential test in athletes, was not used. We recommend that this test should be used in the evaluation of balance in athletes by ensuring standardization in physical conditions in future studies. Another limitation of our study is the short-term one-time measurements of adolescent volleyball players with or without post-COVID-19. Because the study was planned as a cross-sectional study. Cross-sectional studies cannot reveal a cause-effect relationship. Therefore, a longitudinal study can confirm the cause-effect relationship. Considering that COVID-19 affects adults more, we recommend that long-term follow-up studies should be conducted to detect problems that may arise in these children in the future.

Adolescent volleyball players without post-COVID-19 had a higher anxiety score than those with post-COVID-19. It is pleasing that kinesiophobia, perception of dyspnea in daily living activities, pain, fatigue, depression, stress, static balance, and dynamic balance problems are not seen in children who have had mild COVID-19 during the prolonged COVID-19 pandemic period. This makes us think that the devastating and lasting effects of the pandemic on human health in the early stages diminished in the second year of the pandemic. Considering the high rates of kinesiophobia, pain sensation at rest, pain during activities, fatigue at rest, fatigue during activities, depression, anxiety, and stress in adolescent volleyball players with and without COVID-19, regardless of having post-COVID-19, we recommend that children should be evaluated with multidisciplinary approaches and referred to psychological and physical activity counseling when necessary.

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Original Research

The Hormonal Status Comparison of Unilateral and Bilateral Adrenal Adenomas: Are They the Same?

Burak Özbaş[1], Asena Gökçay Canpolat[2], Cansu Özbaş[3], Demet Çorapçioğlu[2], Mustafa Şahin[2]

[1] Department of Endocrinology and Metabolic Diseases, Dr Abdurrahman Yurtaslan Oncology Research and Training Hospital Ankara, Turkey
[2] Department of Endocrinology and Metabolism, Ankara University, School of Medicine, Ankara, Turkey
[3] Department of Public Health, Gazi University, School of Medicine, Ankara, Turkey

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Correspondence
Burak Özbaş
Address: Department of Endocrinology and Metabolic Diseases, Dr.Abdurrahman Yurtaslan Oncology Research and Training Hospital Ankara / Turkey
Email: drburakozbas@hotmail.com

ABSTRACT

Objective: It is not yet clear whether unilateral/bilateral adenomas are different in terms of both functionality and etiology. We investigated whether there were differences in hormonal profiles and evaluate the cortisol secretion profiles of unilateral and bilateral adenomas.

Material&Methods: Hormonal secretory profiles and clinical features of patients with adenomas were collected. Detailed evaluation was made in terms of hypercortisolemia.

Results: Of the 184 patients examined, 140 had unilateral and 44 had bilateral adenomas. 73% of the patients were female and the mean body mass index was 34±8.1kg/m^2. The mean age was 57.1±9.8 years. The average size of the adrenal masses was 23.3±10.5mm. While 83% of the evaluated adenomas were nonfunctional, ACS was found in 11% (n:20), hyperaldosteronism in 4% (n:8), and pheochromocytoma (PCC) in 2% (n:3) of the patients. The prevalence of ACS in bilateral/unilateral adenomas was 20.5%/7.9%, respectively. While serum adrenocorticotropic hormone level (25.6±16.6vs19.3±15µg/dL), urinary free cortisol level (162.3±108.3vs243.3±234.2µg/day), and low-dose-dexamethasone-suppression-test results (1.6±1.9vs1.73±1.7µg/dL) were not statistically different, the only difference between unilateral and bilateral adenomas was in serum DHEA-S level (141.4±85vs77.7±73.8 µg/dL, p:0.003).

Conclusion: Although there is no significant difference between the two groups in terms of clinical findings, it is clear that ACS is more prevalent in bilateral adenomas than unilateral. Because of the negative effects of long-term hypercortisolism, precise management of ACS is noteworthy. The evaluation of ACS should be done more carefully in bilateral adenomas considering that ACS is more in bilateral adenomas than unilateral. According to our findings, we also suggest that DHEA-S may be an indicator for ACS.

Keywords: autonomous cortisol secretion, bilateral adrenal adenomas, Dehydroepiandrosterone Sulfate

INTRODUCTION

Adrenal incidentalomas are tumors of the adrenal gland, mostly found incidentally in imaging modalities of unrelated purposes and greater than 1 cm. The more frequent use of imaging methods such as magnetic resonance imaging (MRI) and computerized tomography (CT) has led to an increased incidence of adrenal incidentalomas [1]. The incidence of adrenal incidentalomas is about 3 % in the middle-aged patient population, whereas it

reaches up to 10% in elderly patients [2].

Adrenal incidentalomas, mostly unilateral, can be bilateral in 10-21% of various studies [3-5]. Although there is much known about unilateral adenomas, there is less information about bilateral adenomas. Interestingly, bilateral adenomas are more common than having two or more adenomas in the same adrenal gland [6]. In a few published articles, bilateral incidentalomas of adrenal glands were different from unilateral in terms of both functionality and etiology [3,7]. It has also shown that if the mechanism had been the same, the prevalence of adenomas in both adrenal glands would be much lower than in the current situation [6]. The most common causes of bilateral adrenal masses are metastases, primary bilateral macronodular hyperplasia, and adenomas [8].

When these frequently encountered lesions are observed in imaging techniques, there are two primary questions to be answered. These questions are 1) Does it have malignant potential and 2) Does it have no hormonal function? [8].

Malignant masses in the adrenal gland may be either primary carcinoma of the adrenal gland or metastases of various cancers. Although primary adrenocortical carcinoma (ACC) is extremely rare (0.72 cases per million), up to 10% of these cases are bilateral. The point of attention in metastases in the adrenal gland is the risk of bilaterality and the potential for adrenal insufficiency [9]. When adrenal incidentalomas are evaluated in terms of functionality, while only a small proportion have apparent hormone secretion and associated clinical stigmas, the vast majority are nonfunctioning and asymptomatic. However, several studies in the last decades have shown that some of these non-functional and asymptomatic tumors have hormone secretion, particularly cortisol [10,11]. Excessive cortisol release without evidence of clinical symptoms was called subclinical Cushing's syndrome or subclinical hypercortisolemia in previous years and was first described by Charbonnel et al. [11]. However, it was thought that these nomenclatures did not reflect the disease condition, and it was named autonomic cortisol secretion (ACS) in 2016 [12]. It was shown that the risk of fragility fractures, arterial hypertension, diabetes mellitus (DM), and metabolic syndrome is increased in ACS [13,14]. In addition to that, improved DM, hypertension, lipid metabolism, and obesity were observed in affected patients after unilateral adrenalectomy but not for osteoporosis in a prospective study [15]. In a meta-analysis published in 2016 comparing surgery and conservative treatment, the patients in the surgical arm had higher recovery rates in DM and hypertension, while there were no significant differences in the improvement of dyslipidemia and obesity [16]. Moreover, another critical aspect is that ACS is much more common than adrenal Cushing's syndrome with a wide range of frequency (5-30%) depending on the criteria used for ACS diagnosis in various studies [17].

There is a current trend for bilateral and unilateral incidentalomas to be evaluated as different entities in terms of origin and functionality in recent years. Therefore, we retrospectively evaluated our cases to compare these unilateral and bilateral adrenal masses regarding hormonal and malignant potentials. We also evaluated the frequency of ACS in our cohort.

Main Points;

- Adrenal adenomas are detected bilaterally between 10-20% and they are thought to differ from unilateral adenomas in terms of hormonal functionality.
- In our study, cortisol hypersecretion was found to be more common in bilateral adenomas.
- The risk of cortisol hypersecretion is higher, especially in patients with low dehydroepiandrosterone sulfate (DHEA-SO4) measured at baseline tests.
- Treatment approach in patients with bilateral adenoma and cortisol hypersecretion is still unclear and prospective studies are still needed on this subject.

MATERIALS AND METHODS

Patients

In this study, 204 patients admitted to tertiary endocrinology clinics between 2005 and 2014 with the diagnosis of adrenal incidentaloma were evaluated. Presence of overt Cushing syndrome or Cushing's disease, diseases (alcoholism, major depressive disorder, renal and hepatic failure) or drugs that affect the dexamethasone suppression test (DST) and steroid metabolism, and patients with a history of chronic steroid intake, oral contraceptives, and postmenopausal hormonal replacement treatment were excluded (Figure 1). Twenty patients were excluded according to radiological findings such as non-adenoma adrenal pathologies. Patients with a history of malignancy were also excluded. The remaining 184 patients were divided into two groups: unilateral and bilateral adenomas. The study was approved by the local Ethical Committee of Ankara University Faculty of Medicine (04-179-15/9/3/2015).

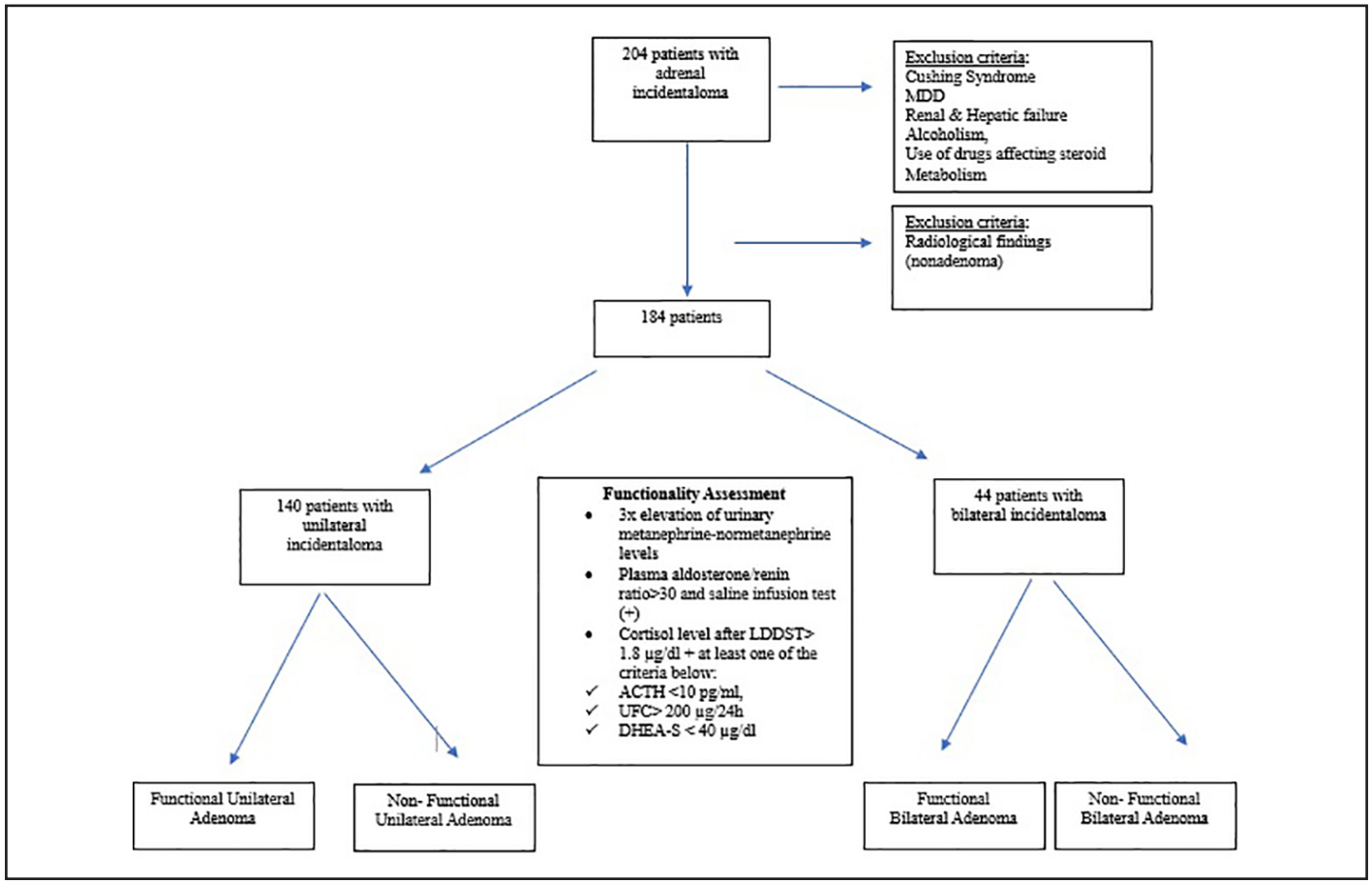

Figure 1. Flow chart of patients included in the study
Abbreviations: **MDD:** Major Depressive Disorder, **LDDST:** Low Dose Dexamethasone Suppression Test, **ACTH:** Adrenocorticotropic hormone **UFC**: Urinary Free cortisol, **DHEA-S** Dehydroepiandrosterone-Sulfate

Hormonal and Biochemical Assessment

Blood samples were obtained from each patient in the morning after 12 h of fasting to measure routine complete blood count (CBC) analysis and biochemistry panel.

Serum adrenocorticotropic hormone (ACTH), cortisol, dehydroepiandrosterone sulfate (DHEA-S), total testosterone, aldosterone levels, plasma renin activity, urine metanephrine, and normetanephrine levels, and urinary free cortisol levels were also measured to assess the hormonal activity.

Serum cortisol concentrations were ascertained by immunoenzymatic assay (Beckman Coulter, Access Immunoassay Systems, Access cortisol assays, USA). The intra-assay coefficients of variation (CV) were less than 5%. We ascertained urinary free cortisol by radioimmunoassay (DIAsource Immunoassays S.A., Belgium), and the intra-assay CV was less than 7%. The serum ACTH concentration was measured by electrochemiluminescence immunoassay (Roche Elecsys 2010 analyzer, Roche Elecsys-ACTH), and the intra-assay CV was less than 6%. DHEA-S was measured using diagnostic kits obtained from Beckman Coulter by chemiluminescent immunoassay (Beckman Coulter, Access Immunoassay Systems, USA), and the intra-assay CV was less than 8.3%.

Free cortisol measurement in 24-hour urine and DSTs were conducted in patients suspected to have Cushing's syndrome and ACS via 1 and 2 mg.

At least one of the following criteria was adopted to diagnose ACS as the cortisol value was above 1.8 µg/dl after 1 mg DST: ACTH <10 pg/ml, urinary free cortisol (UFC) > 200 µg/24h, DHEA-S < 40 µg/dl [5].

Statistical Analysis

Data were statistically analyzed using SPSS (SPSS for Windows, Version 15.0. Chicago, SPSS Inc.) statistical software. The data were expressed as mean ± SD. The distribution of parameters among groups was investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test). Categorical parameters were evaluated using the chi-square test. Since the distribution of these subdivisions was normal according to the visual and analytical methods, two groups were compared using independent T-tests, and one-way analysis of variance (ANOVA) tests were performed comparing four groups for continuous variables. An overall p-value of less than 0,05 was considered to show a statistically significant result. When overall significance was observed, the pairwise post hoc test was performed using the Bonferroni test. A logistic regression model was created and used for multivariate analysis to evaluate the risk factors for ACS development. In the model created, bilateral adrenal adenoma development was evaluated in groups with autonomous cortisol secretion according to age and BMI.

RESULTS

Patient characteristics

184 patients were included in the analysis. Written informed consent was obtained from all patients. The male-to-female ratio was M/F: 27/73% (48 male and 136 female), the mean age was 57.1 ± 9.8, and the mean body mass index (BMI) was 34 ± 8.1. In 88 % of the patients, the diagnosis and follow-up of the adrenal adenoma were performed by CT, while the method used in 12 % of the patients was MRI. The average size of the adrenal masses was 23.3±10.5 mm. While 83 % of the evaluated adenomas were nonfunctional, ACS was found in 11% (n:20), hyperaldosteronism in 4% (n:8), and pheochromocytoma (PCC) in 2% (n:3) of the group. The patients were evaluated with either CT or MRI twice a year for follow-up of tumor growth. No increment in tumor sizes was noted during follow-up. The two patients were operated on because the tumor size (with a great dimension of 55 mm) did not reveal malignant histopathology. PCC was detected in a patient who was operated on for a 60-mm unilateral adenoma.

Evaluation of unilateral and bilateral adenomas

No significant difference was found between the two groups in terms of age, gender, BMI, and mass size, as shown in Table 1. There was no significant difference between the two groups for the low-dose dexamethasone suppression test (LDDST), UFC, and ACTH. On the other hand, DHEA-S was found to be lower in bilateral adenomas than in unilateral adenomas (77.7 ± 73.8 vs. 141.4 ± 85, p: 0.003).

Functional evaluation of 140 patients with unilateral adrenal incidentaloma revealed ACS in 11 patients, Conn's syndrome in 6 patients, and PCC in 2 patients. Of the 44 patients with bilateral adrenal adenoma, 9 had ACS, 2 had Conn's syndrome, and one had PCC. In our evaluation of 184 included patients, ACS was present in 7.9 % (11/140) and 20.5 % (9/44) in unilateral and bilateral adrenal adenoma patient groups, respectively. This result was statistically significant (p= 0.027), and the odds ratio was calculated to be 3.01 (CI 1.1-7.8) for comparing the two groups. As shown in Table 2, this ratio was 3.07 when age and BMI-adjusted values were used. However, when we investigated whether this situation had a clinical reflection in patients, no significant difference was found between the two groups in terms of metabolic disorders due to cortisol excess such as hypertension, IFG, DM, and dyslipidemia.

The evaluation of patients with and without ACS

Considering the clinical features of the patients (Table 3), there was no difference between patients with ACS and patients with non-functional adrenal adenomas in terms of hypertension (55% vs. 31%, p:0.06) and dyslipidemia (73.7% vs. 70.1%, p:0.74) frequency. However, it was observed that IFG/DM was more common in patients with ACS (45% vs. 17.4% p:0.01). Although the mean greatest dimensions of adenomas with ACS were larger than non-functional adenomas, there was no statistically significant difference (26.4±11 vs. 22.5±10.1, respectively p:0.11). In addition to post-LDDST nonsuppressed cortisol (4.54 ± 3.5 vs 1.16 ± 0.5; p< 0.001) in patients with ACS, a significant decrease in DHEA-S (61.4 ± 38.5 vs 106.6 ± 79 p= 0.02) was observed.

Evaluation of bilateral and unilateral adenomas according to the presence of ACS:

Considering the clinical characteristics of the patients; there was no significant difference in age, gender, mass size, BMI, dyslipidemia, DM, and hypertension in the subgroup analysis of patients who were divided into four groups according to the presence of bilaterality and ACS (unilateral ACS -, unilateral ACS +, bilateral ACS -, bilateral ACS +) (Table 4). Besides these, in the examination of patients' laboratory characteristics, the cortisol values after LDDST (1.17 ± 0.5; 5.73 ± 3.9; 1.1 ± 0.4; 3.1 ± 2.7 respectively, p<0,001) and DHEA-S (141.7 ± 87; 62.1 ± 35.3; 69.4 ± 46; 40.8 ± 43.2 respectively, p:0.01) measurements were found to be different. In the binary analysis, as expected,

the cortisol value after LDDST was found to be significantly higher in the ACS (+) than in the ACS (-) two groups. In addition, DHEA-S levels were lower in bilateral adenomas than in unilateral ACS (-) adenomas (Table 4).

Logistic Regression Analysis: In age- and BMI-adjusted logistic regression analysis, bilaterality was correlated with ACS (p=0,039).

DISCUSSION

The frequency of adrenal incidentalomas has increased since it was first described in 1941. Although they were initially thought to be hormonally nonfunctioning, up to 20% of adrenal incidentalomas secrete hormones [15]. ACS is reported in adrenal incidentalomas with a 5–30% prevalence, depending on the screening procedures in numerous studies [17]. Numerous studies have shown that even if ACS does not lead to prominent clinical findings, it may cause comorbidities of cortisol release. Thus, this clinical condition necessitates the diagnosis and strict follow-up of this entity.

One of our major findings was the higher frequency of ACS in patients with bilateral adrenal adenoma than unilateral adrenal adenoma (20,5% vs. 7,9 %, respectively, p: 0.027). Paschou and colleagues reported that ACS prevalence was increased in bilateral adrenal incidentalomas vs. unilateral adenomas in a recent meta-analysis. They argued on the difference in cortisol chronobiology regulation between unilateral adrenal incidentalomas and bilaterals [18]. Current genetic trials conducted within the past few years have found that etiologies of bilateral adrenal adenomas might be different from one another [6,19]. Bilateral and unilateral adenomas also have different molecular backgrounds and may impact cortisol-related comorbidities [20].

The increasing prevalence of ACS in bilateral adrenal tumors poses a challenge for clinicians to diagnose [20]. Although there is no radiological guidance for bilateral incidentalomas, hormonal evaluation becomes more critical in their evaluation and follow-up. Moreover, ACS diagnosis relies on clinical evaluation, and the nature of the disease is asymptomatic; specific parameters to assess this entity are an obligation. Until now, some clinical biomarkers and tests have been utilized to differentiate between cortisol- and non-secreting adenomas, especially in patients with bilateral adrenal incidentalomas. Early morning ACTH, urinary-free cortisol, midnight salivary cortisol, and LDDSTs are the most common tests studied for ACS. Because of its short half-life and pulsatile secretion, ACTH has low sensitivity and specificity in detecting ACS [21]. Although plasma ACTH levels are generally low in ACS, there is an overlap with ACTH levels in healthy individuals [22]. Also, 24-hour urinary free cortisol (UFC) has poor specificity and false positivity in detecting ACS [23]. In our study, we could not find a difference in ACTH, urinary free cortisol, and LDDST between unilateral and bilateral adrenal adenomas, and only LDDST and DHEAS were different among the non-functional and ACS groups.

Other potential markers were proposed for a possible ACS marker in patients with AI because of all the above-mentioned circumstances. DHEAS was one of the most implemented markers for the diagnosis of ACS. The proposed mechanism of the usage of this marker is the reductive effect of the central suppression of ACTH on DHEAS [24]. It is a more reliable test because of its prolonged half-life and stable level during day [23]. Previous studies suggested suppressed levels of DHEAS as a potential indicator of ACS [5,25]. Yener et al. reported an age-unadjusted DHEAS threshold of 40.0 mcg/dL with a sensitivity of 68% and a specificity of 75% for the diagnosis of ACS [5]. We found a significant difference between unilateral adenomas vs. bilateral adenomas and nonfunctional adenomas vs. ACS. Bilateral ACS had the lowest levels of DHEAS with a mean level of 60.8 ± 43.2 μg/dL (p:0.01). This finding supports the use of DHEAS as a diagnostic criterion for ACS, especially for bilateral adrenal incidentalomas. Despite nonsuppressed cortisol values after 1 mg DST being the most accurate test to diagnose ACS, we required the presence of at least one additional hormone abnormality (ACTH suppression, low DHEA-S, high UFC).

Another significant finding of our study was that there was no difference in mass size among groups of patients with and without ACS. The mass sizes were larger than nonfunctional adrenal masses, but they did not reach statistical significance. Most previous studies reported larger adrenal masses in patients with ACS [26-28]. They all suggested a relationship between cortisol secretion and mass volume in ACS. As the tumor diameter increases, the risk of autonomic cortisol-release increases in adrenal adenomas [26]. In contrast to these reports, we did not find such an association between mass size and hypercortisolism, which was compatible with a few previous studies [29,30].

Although the ACS rate in patients with bilateral adenoma

is higher than that in patients with unilateral adenoma, this does not appear to be clinically relevant. No statistically significant difference was found between the two groups in terms of diseases such as hypertension, DM/Impaired Fasting Glucose (IFG), and dyslipidemia, which we expect to occur due to hypercortisolemia. When the effects of ACS on clinical features were investigated, there was no difference in HT and dyslipidemia between patients with or without ACS, whereas DM/IFG was significantly higher in the ACS group. The most common clinical features of ACS are HT and impairment of glucose metabolism. There is an association between ACS and these metabolic derangements resulting from the direct and indirect effects of cortisol on the vascular system [21]. We could not find such an association for HT. There were also few studies reporting no relationship between ACS and HT [31,32]. The attributed mechanism for this finding was thought to be associated with a higher cut-off value of LDDST, but this could not be implemented in our findings because of our lower cut-off value for LDDST. We can only hypothesize that there might be cyclic secretion of cortisol in our ACS group, although we could not obtain such a finding. Also, the duration and degree of patients' exposure to high-dose cortisol may be a possible factor. Unfortunately, we do not have the long-term results of these patients because of the retrospective design of the study. Clinical manifestations are likely to occur in the long term in patients with autonomous cortisol secretion who remain untrained and untreated.

Although the primary pigmented nodular adrenocortical disease may rarely be seen as adenoma [33], our cases were evaluated by two different experienced radiologists and determined as adenomas. In these cases, biopsy or surgery may be the only way to make a definitive differential diagnosis. As we already know, adrenal biopsy is not generally the preferred method for diagnosing benign diseases of the adrenal gland, and even in biopsies performed to confirm the diagnosis of malignancy, high diagnostic success was not achieved.

One of the difficulties in the management of bilateral adrenal adenomas is the optimal treatment approach. In our patient group, only one patient undergoing bilateral adenoma underwent surgery. Today, surgery is still the only curative treatment for Cushing and ACS. However, postoperative morbidities of bilateral adrenalectomy are reported to be high (18%) in a previous paper [34]. In this case, an alternative to bilateral adrenalectomy was the follow-up of these patients without treatment. However, surgery benefits have been shown in patients with ACS in a prospective study [15]. The third option in these patients is to determine the side with dominant cortisol release and perform unilateral adrenalectomy. Similar to the adrenal venous sampling performed in primary hyperaldosteronism, it can be determined which adrenal glands dominantly secrete cortisol by measuring cortisol from both adrenal veins. In an article published by Young et al. evaluating ten patients with bilateral adenoma, it was seen that cortisol was secreted from one side in 5 of 10 patients [27]. No recurrence was detected during follow-up after unilateral adrenalectomy. However, this method is not standardized yet and more extensive prospective studies are needed.

No primary adrenocortical carcinoma was found in the patient group we examined. This may be because primary ACC cases, whose mass size reaches huge diameters at the time of diagnosis, are primarily evaluated in surgical clinics, and patients with a pre-diagnosis of adrenal gland metastasis are primarily evaluated in oncology clinics where they are followed up with a diagnosis of cancer. This data was consistent with previous studies, and studies in endocrine clinics showed that primary ACC and adrenal metastasis rates were low, and these rates may differ from those in surgical clinics [4,8]. In Dunnick's study, in which radiological features of adrenal masses were examined, it was seen that 10% of primary ACCs were bilateral [35]. There was no statistically significant difference in malignancy in the two patient groups we compared ($p>0,005$). However, it is not easy to say whether or not bilaterality is a risk factor for primary ACCs as it has an extremely low (0.72 per million) incidence [36]. Moreover, a study in which bilateral masses were followed for 12 years failed to show any evidence of an increase in the risk of long-term malignancy in bilateral masses [37].

There was a female predominance (136/48) in the patients included in our study. This predominance has also been observed in other retrospective studies of adrenal incidentalomas but not in autopsy studies [2,5,38]. Although there is a review showing that this gender difference is not only in adenomas but in all adrenal tumors, the factors causing this difference have not been fully elucidated, and it was thought that the reason why adenoma is more common in women may be due to the more frequent use of abdominal imaging in women [38].

The limitations of our study were the retrospective design of the study and the lack of other supportive measures such as midnight

cortisol or salivary cortisol measurements. We did not evaluate patients for cardiovascular status or bone metabolism because of the possible deleterious effects of cortisol on the cardiovascular system and bone metabolism. Another limitation was the absence of a surgical evaluation of ACS patients. However, there were no clear surgical indications for our ACS patient group.

In conclusion, the presence of bilaterality is essential in the evaluation of adrenal adenomas. Although there was no significant difference in the size of the adenomas in the current study, functional evaluation became more critical in adenomas with both bilaterality and a size of more than 2 cm. Another important point in ACS patients is that the metabolic derangement may not always present in these patients. Therefore, the decision for the presence/absence of ACS should never be made solely based on clinical findings, and hormonal examination should be performed. DHEA-S, which has a low plasma level due to autonomous cortisol release, should be examined in the functional examination of patients with adrenal adenomas. Finally, why autonomous cortisol secretion is more common in bilateral adenomas is still unknown. Also, the treatment approach in these patients could not be clarified. Hence, more prospective studies are needed in this field.

Conflict of Interest: Authors have no conflict of interest to declare.

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Ethical Statement: The study was approved by the Clinical Research Ethical Committee of Ankara University Faculty of Medicine (04-179-15/9/3/2015).

Author Contributions: BO, AGC, and MS contributed to the study design. BO and CO contributed to the acquisition of data. BO, AGC, CO, and MS contributed to data analysis and interpretation. BO and AGC contributed to the drafting of the manuscript. BO, AGC, DC, and MS contributed to revise the manuscript. All authors have read and approved the final version of the manuscript.

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Original Research

Morphological and Morphometric Variations of the Hyoid Bone in Anatolian Population

Gkionoul Nteli Chatzioglou [1], Elif Toklu [1,2], Elif Bayraktar [2], Ahmet Ertaş [3], Ayşin Kale [2], Osman Coşkun [2], Adnan Öztürk [1], Özcan Gayretli [2]

[1] Department of Anatomy, Faculty of Medicine, Istanbul Health and Technology University, Istanbul, Türkiye
[2] Department of Anatomy, Faculty of Medicine, Istanbul University, Istanbul, Türkiye
[3] Department of Anatomy, Istanbul University, Cerrahpaşa Faculty of Medicine, Istanbul, Türkiye

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Correspondence
Gkionoul Nteli Chatzioglou, PhD
Address: Department of Anatomy, Faculty of Medicine, Istanbul Health and Technology University,
İmrahor St. No:82, 34015 Beyoglu, Istanbul / Türkiye
E-mail: gkionoul.chatzioglou@istun.edu.tr

ABSTRACT

Objective: The morphological and morphometric variations of the hyoid bone (os hyoideum) are known to be significant in cervical surgeries and also serve as important evidence in forensic cases involving hanging and strangulation. The aim of this study is to investigate the morphological and morphometric differences of the hyoid bone.

Methods: Sixty-four adult hyoid bones of unknown age and gender were used in our study. Ethical approval for the study was obtained from the Istanbul Faculty of Medicine Clinical Research Ethics Committee (date/number: 15.12.2021/632888). The bone shape variations were classified into four main groups: D, U, B, and V types according to the morphometric measurements of the hyoid bone. Also the hyoid bones were evaluated based on their symmetry and isometry properties. Morphometric measurements were analyzed for reliability and repeatability using TEM, rTEM, and R tests, with the same person measuring twice. Measurements were calculated using the Image J program. The data were analyzed using SPSS v.21.

Results: The percentages of D, U, B, and V types were found to be 53.84%, 23.07%, 15.38%, and 11.53%, respectively. Among the hyoid bones, 34 (53.12%) were found to be asymmetrical, 30 (46.88%) symmetrical, 35 (54.69%) anisometric, and 29 (45.31%) were isometric.

Conclusion: Our study's results indicate that the hyoid bone of Anatolian individuals exhibits morphological differences compared to other populations. Understanding the morphological and morphometric values of the hyoid bone can contribute to clinical and forensic applications.

Keywords: forensic application, hyoid bone, morphometry, morphology, variation

INTRODUCTION

The hyoid bone is a unique and intricate structure located in the neck, situated at the base of the skull and above the thyroid cartilage. Unlike other bones in the body, the hyoid bone does not articulate with any other bone, making it the only free-floating bone in the human skeleton. Its distinct shape and position play a crucial role in various physiological functions, including speech, swallowing, and the stability of the neck. The hyoid bone is named from its resemblance to the Greek "*ύψιλον* (υ)» (upsilon), letter which is the 20th letter of the modern Greek alphabet. It is also called the lingual bone, because it supports the tongue and gives attachments to its numerous muscle. It is a bony arch, shaped like a horseshoe, and consisting of five segments, a body, two greater cornua,

and two lesser cornua. Moreover, morphologically, the hyoid bone resembles a horseshoe-shaped structure with a body and two pairs of projections known as horns. The body of the hyoid bone is centrally located and slightly curved, with a superior convexity and an inferior concavity. The superior surface of the body presents a midline ridge called the median sulcus, which serves as an attachment point for various muscles and ligaments. The horns of the hyoid bone project outwards and are named based on their anatomical positions. The greater horns, also known as the cornua, extend posteriorly and laterally from the body. They are relatively larger and serve as crucial points of attachment for muscles, including the muscles of the tongue and larynx. The smaller, more superior pair of projections is called the lesser horns, which are connected to the body via thin bony stalks [1-5].

The hyoid bone holds significant importance in the field of medicine due to its various functions and clinical implications. It plays a crucial role in swallowing, speech production, airway management, forensic medicine, surgical procedures, radiological imaging, and anthropological studies [6,7]. In terms of swallowing and speech, the hyoid bone acts as an anchor for the muscles involved in these processes, ensuring proper coordination and movement. Evaluating the position and function of the hyoid bone is essential in diagnosing and managing swallowing disorders (dysphagia) and speech impairments. For airway management, the hyoid bone's relationship with the upper airway and laryngeal structures is crucial. It contributes to maintaining a patent airway during respiration, making it important in procedures such as intubation, tracheostomy, and surgical interventions involving the airway [7-9]. In forensic medicine, the hyoid bone can provide valuable evidence in determining the cause and manner of death. Its examination for fractures or trauma helps forensic experts establish the presence of external pressure or force, especially in cases involving suspected strangulation or asphyxiation. It is involved in various surgical procedures, particularly in head and neck surgery. Surgeries like hyoid suspension or hyoid advancement can address conditions like obstructive sleep apnea or improve airway stability [10-12]. Understanding the anatomy and biomechanics of the hyoid bone is crucial for the success and safety of these surgical interventions. Radiological imaging techniques, such as X-rays, Computed Tomography (CT) scans, and Magnetic Resonance Imaging (MRI), allow for detailed visualization and assessment of the hyoid bone. Radiological evaluation aids in diagnosing fractures, tumors, and other pathological conditions affecting the neck region. It plays a significant role in treatment planning and patient management [13]. In anthropological studies, the hyoid bone provides insights into human evolution, population genetics, and species identification [14]. Variations in its morphology among different populations or species contribute to our understanding of evolutionary patterns and help in identifying skeletal remains [15-18].

The aim of the study is to investigate the morphological and morphometric properties of the hyoid bone. By analyzing its shape, size, and structural characteristics, the study aims to contribute to our understanding of its variations and potential clinical implications. This research can further enhance our knowledge of the hyoid bone's role in medicine and potentially lead to advancements in diagnosing and managing conditions related to its function and structure.

Main Points;

- Examination of the morphology of the hyoid bone according to morphometric measurements.
- Identification and demonstration of variations of the hyoid bone.
- Precision assessment of hyoid bone measurements.

MATERIALS AND METHODS

The hyoid bone of 64 adult cadavers from the Department of Anatomy, Istanbul Medical Faculty was included in our study. Ethical approval for the study was obtained from the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 2021.12.15, Approval Number:632888). The morphometric measurements of the parameters in our study were made from the anterior lateral and superior aspects of the hyoid bone.

The following parameters were measured from the anterior aspect of the hyoid bone:

- The central height of the body of the hyoid bone (Figure 1A)
- The maximum height of the body of the hyoid bone (Figure 1A)
- The width of the body (corpus) of the hyoid bone (Figure 1B)

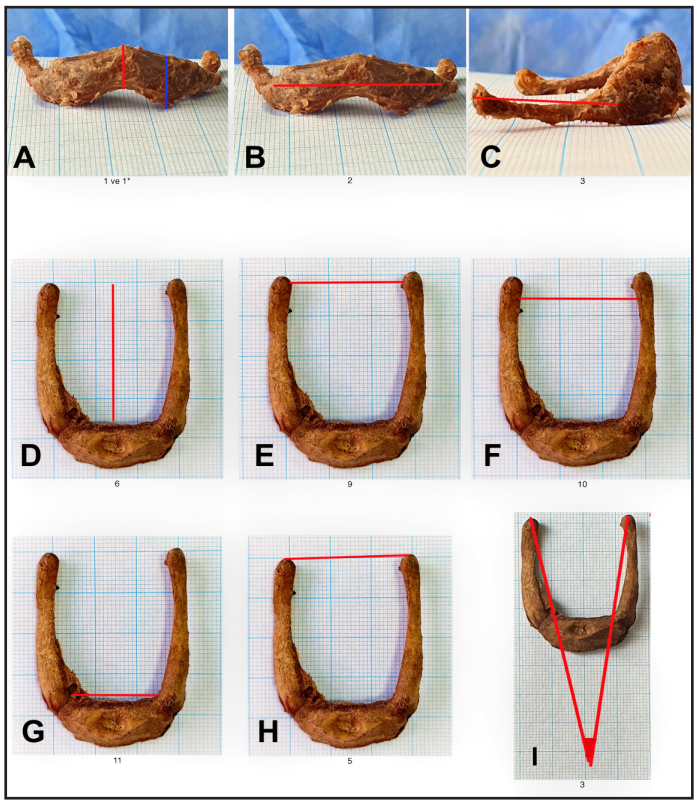

Figure 1. The morphometric measurements of hyoid bone from anterior (A, B and C) and superior (D, E, F, G, H and I) aspects. A. The central heigth of the body of hyoid bone (red vertical line), corpus max yükseklik (blue vertical line) and the maximum height of the body of hyoid bone B. The width of the body of hyoid bone. C. The length of the greater horn of the hyoid bone D. The anteroposterior vertical length of the hyoid bone: the distance between the inner-central side of the body of hyoid bone and the distal ends of the greater horns E. The transverse distance between the tubercles of greater cornua F. The major transverse axis G. The length of the body of hyoid bone H. The transverse distance between the posterior ends of greater horns I. The angle between the left and right greater horns

The following parameters were measured from the lateral aspect of the hyoid bone:

- The length of the greater horn of the hyoid bone (Figure 1C)
- The lateral angle of the greater horn-angulation I (if there is): the angle between the axis of greater horn and the hyoid body plane. In cases where the greater horn was in equal plan with the body of the hyoid bone, no angle measurement was performed (Figure 2A)
- The lateral angle of the greater horn-angulation II (if there is): when the posterior end of the greater horn is in the same plane as the body of the hyoid bone and in contact with the ground, and the angle formed by the section of the greater horn between these two points without contact with the ground (Figure 2B and Figure 3).

The following parameters were measured from the superior aspect of the hyoid bone:

- The anteroposterior vertical length of the hyoid bone: the distance between the inner-central side of the body of hyoid bone and the distal ends of the greater horns. (Figure 1D)
- The transverse distance between the tubercles of greater cornua (Figure 1E)
- The major transverse axis (Figure 1F). The hyoid bones were also assessed based on their symmetry of the major transverse axis. If the midpoint of all transverse diameters was equidistant from the sagittal "y" axis, the bones were labelled as symmetrical; otherwise, they were categorized as asymmetrical according to Papadopoulos et al. [19] (Figure 4)
- The length of the body of the hyoid bone: the length was measured from the inner side of the hyoid bone (Figure 1G)
- The transverse distance between the posterior ends of greater horns (Figure 1H)
- The angle between the left and right greater horns: the angle formed by connecting the midpoints of the anterior and posterior ends of the greater horn (Figure 1I)

Morphometric measurements were performed twice by the same person. The Image J software (Rasband, W.S., ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997–2016) was used to measure the morphometric parameters (Figure 3). The measurements' reliability was assessed using TEM, rTEM, and R methods. The Technical Error of Measurement (TEM) quantifies the error magnitude, similar to the standard deviation, but it considers both measurement values. On the other hand, the Relative Technical Error of Measurement (rTEM) expresses the error size relative to the measurement size and is represented as a percentage. Lastly, the Coefficient of Reliability (R) is a reliability coefficient that reflects the proportional variation within an individual, independent of measurement error. Its value ranges from 0 (not reliable) to 1 (completely reliable).

The morphological features of the hyoid bones were classified into four main groups (Figure 5) as "D (deviating), H (horseshoe shape)/U (upsilon shape), B (boat shape) and V (triangular or resembling the V letter) types" according to the findings of the morphometric measurements. The hyoid bones' shapes

were observed and categorized using the system proposed by Papadopoulos et al. According to this system, the bones are classified as follows:

- If the anterior part of the bone forms a half circle and its diameter is approximately the same as the posterior transverse diameter, it is referred to as the "U-Type" (Figure 5A).
- The "B-Type" resembles the transverse section of a boat, with its diameter coinciding with the major transverse axis (Figure 5B).
- If the anterior part is a half circle and one or both greater horns deviate to one or the other side at the posterior end, it is classified as the "deviating-D-Type." (Fig 5C)
- If the bone has a triangular shape or resembles the letter V, it falls under the "V-Type." (Figure 5D).

Anisometric hyoid bone (if there is): a bone is considered isometric when the tips of both greater horns align on the same x-axis of the scale, regardless of whether the lengths of the horns are the same. On the other hand, if the tips of the greater horns do not align on the same x-axis and the transverse line from the tip of the shorter horn crosses the contralateral longer horn, the bone is considered an isometric (Figure 6).

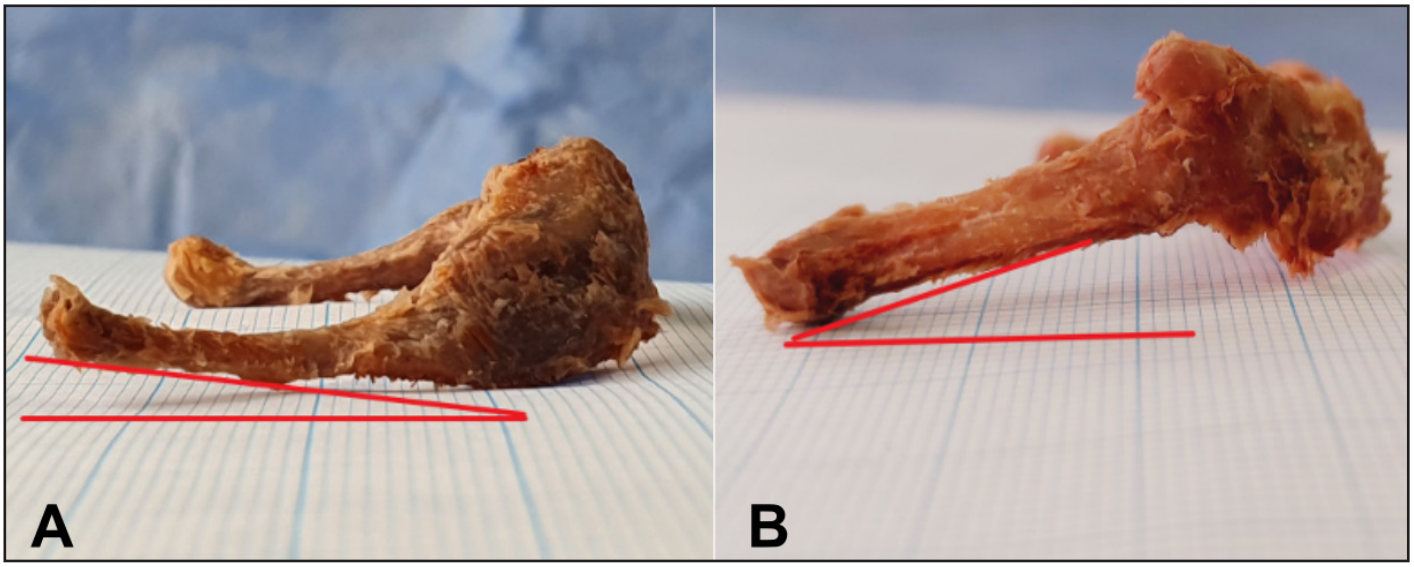

Figure 2. The measurements of hyoid bone from the lateral aspect. A. Lateral angle of the right greater horn of hyoid bone-angulation I. B. Lateral anormal angle of the right greater horn of hyoid bone-angulation II.

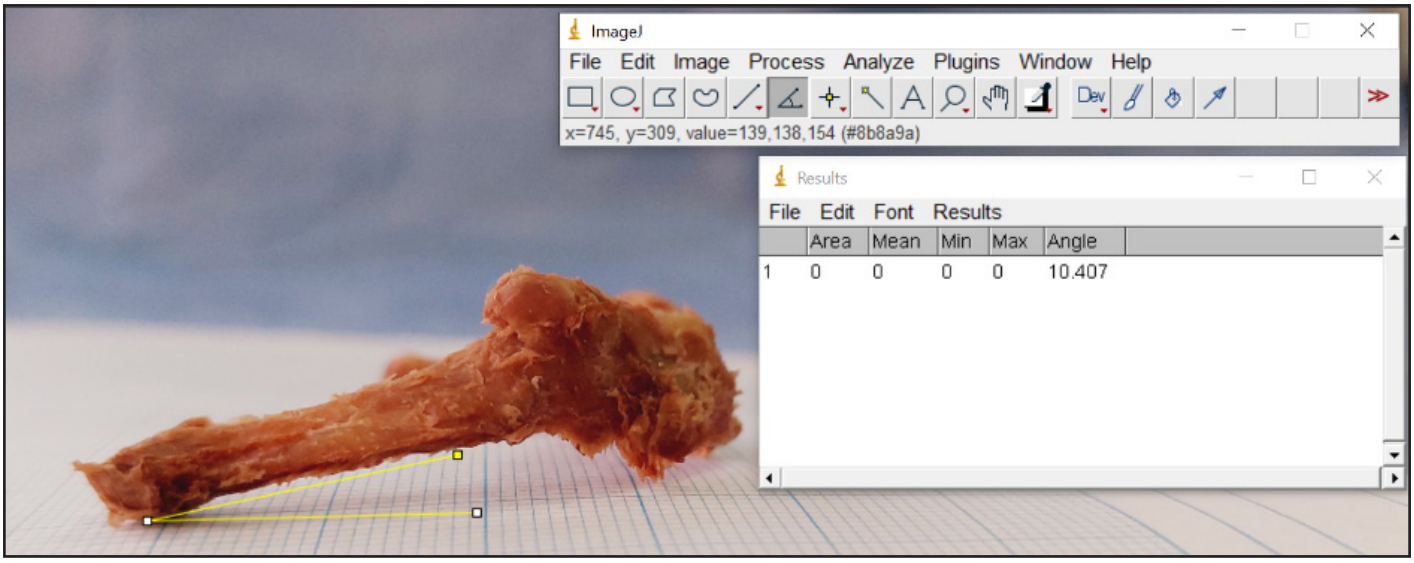

Figure 3. Measurement of right lateral angle of greater horn (angulation II) with Image J method

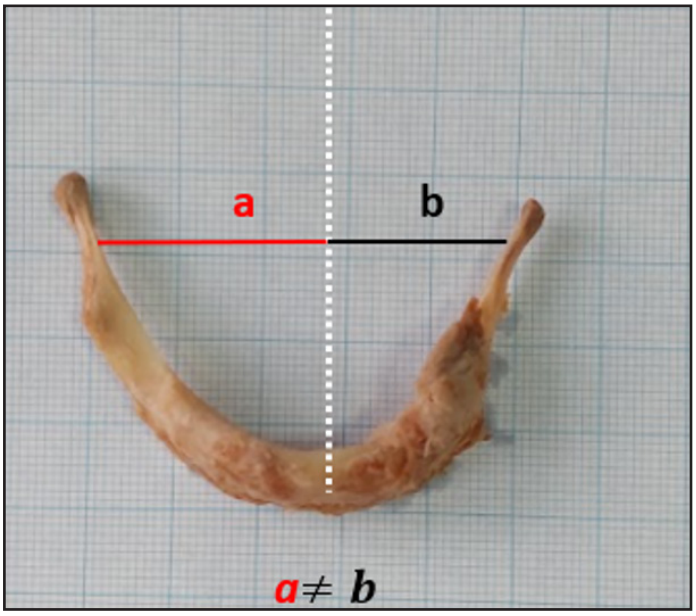

Figure 4. Asymetric hyoid bone. The midpoint of the transverse diameters (red (a) and the black (b) lines) is not equidistant from the sagittal "y" axis (represented by the white dashed line).

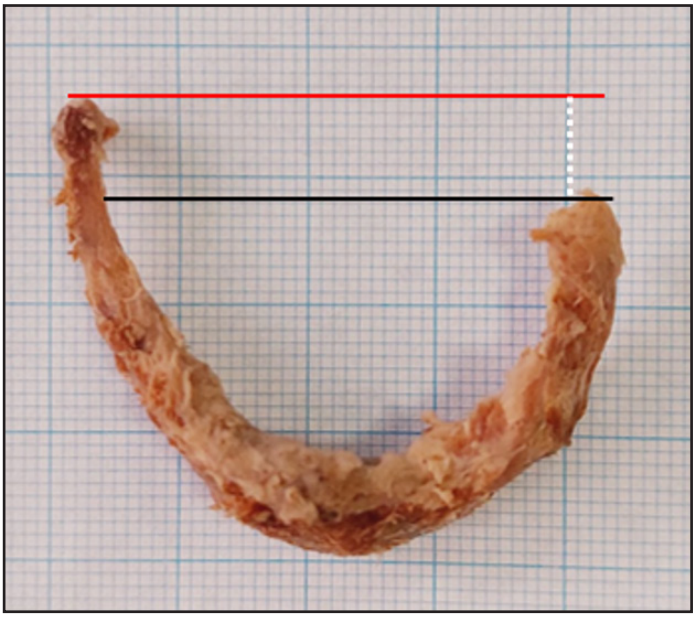

Figure 6. Anisometric hyoid bone. The tips of the greater horns do not align on the same x-axis and the transverse line from the tip of the shorter horn crosses the contralateral longer horn. The abnormal interval (white dashed line) between the posterior end of the right greater horn (red line) and the posterior end of the left posterior horn (black line).

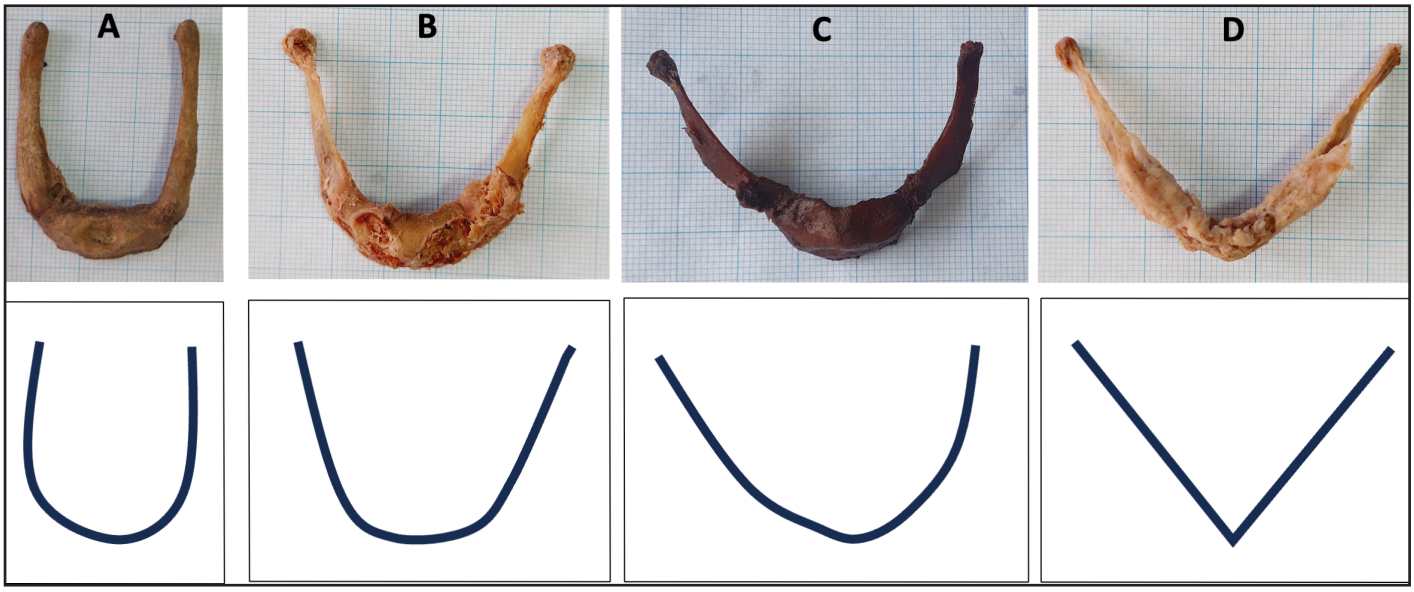

Figure 5. Morphometric measurements of the hyoid bone from the superior aspect for its morphological classification. A- U-type of hyoid bone B. B-type of hyoid bone C. D-type of hyoid bone D. V-type of hyoid bone

RESULTS

The morphological types of the hyoid bone were identified, including the D-type 33 hyoid bones (51.56%), H/U-type 15 hyoid bones (23.43%), B-type 9 hyoid bones (14.06%), and V-type 7 hyoid bones (10.93%) based on the Papadopoulos et al. [19] classification (Figure 5). Apart from the main classification, 34 (53.12%) of the hyoid bones were asymmetric, 30 (46.88%) symmetric; 35 (54.69%) anisometric, 29 (45.31%) isometric. Regarding the morphometric measurements of the hyoid bone, the body of the morphometric features of hyoid bone and the

greater horns of the hyoid bone were measured. The angles between these structures were also included in our study. Additionally, we investigated the variability of the angle of the greater horns, which led to the identification of two distinct tendencies of angulation (Figure 2). These were classified as angulation I and angulation II, with proportions of 30/128 and 59/128, respectively. This intriguing discovery highlights the diverse anatomical characteristics within the greater horn of the hyoid bone, providing valuable insights into its morphological variations. The results of our study related to the morphometric measurements are comprehensively presented in Table 1. Furthermore, morphometric measurements were controlled by TEM, rTEM and R tests in our study (Table 2).

Table 1. The mean morphometric measurements of the hyoid bone

Parameters	n	Mean±SD	Minimum-Maximum	View of hyoid bone
The central heigth of the body of hyoid bone	64*	10.98±1.08 mm	7.67-16.00 mm	Anterior aspect
The width of the body of hyoid bone	64*	23.54±3.52 mm	16.47-30.84 mm	Anterior aspect
The maximum height of the body of hyoid bone	64*	12.55±1.38 mm	9.18-17.42 mm	Anterior aspect
The transverse distance between the posterior ends of greater horns	64*	43.89±8.15 mm	28.80-62.09 mm	Superior aspect
The anteroposterior vertical length of the hyoid bone	64*	28.9±4.05 mm	20.14-41.78 mm	Superior aspect
The angle between the left and right greater horns	64*	40±7.60˚	11.32-60.22˚	Superior aspect
The transverse distance between the tubercles of greater cornua	64*	38.60±7.66 mm	25.02-55.96 mm	Superior aspect
The major transverse axis	64*	38.48±6.04 mm	26.06-53.31 mm	Superior aspect
The length of the body of hyoid bone	64*	19.15±3.31 mm	12.60-25.85 mm	Superior aspect
The length of the greater horn of the hyoid bone	128**	30.27±6.63 mm	22.92-48.31 mm	Lateral aspect
The lateral angle of the greater horn- angulation I	59/128**	7.52±7.73˚	1.63-15.80˚	Lateral aspect
The lateral angle of the greater horn-angulation II	30/128**	13.09±3.89 ˚	1.91-32.72˚	Lateral aspect

SD: standard deviation, **n:** number of smaples * number of hyoid bones, ** number of sides of hyoid bone

Table 2. Precision assessment of hyoid bone measurements

Parameters	n	TEM (mm)	rTEM (%)	R
The central heigth of the body of hyoid bone	26*	2.75	23.44	0.11
The width of the body of hyoid bone	26*	3.36	14.14	0.48
The maximum height of the body of hyoid bone	26*	2.70	24.11	0.15
The transverse distance between the posterior ends of greater horns	26*	0.43	0.97	0.99
The anteroposterior vertical length of the hyoid bone	26*	0.33	1.11	0.99
The angle between the left and right greater horns	26*	0.46	1.09	0.99
The transverse distance between the tubercles of greater cornua	26*	0.48	1.23	0.99
The major transverse axis	26*	0.34	0.88	0.99
The length of the body of hyoid bone	26*	0.36	1.85	0.97
The length of the greater horn of the hyoid bone	52**	1.08	3.52	0.97
The lateral angle of the greater horn- angulation I	21/52**	0.0096	0.12	0.99
The lateral angle of the greater horn-angulation II	12/52**	0.065	0.82	0.99

TEM: Technical error of measurement, **rTEM:** relative technical error of measurement, **R:** coefficient of reli-ability, **n:** number of smaples, * number of hyoid bones, ** number of sides of hyoid bone

DISCUSSION

The Morphology of Hyoid Bone

The hyoid bone, located in the neck, exhibits various morphological variations that can be classified into distinct types. These classifications provide insights into the diversity of shape and structure observed in the hyoid bone across individuals and species. Studying the variations of hyoid bone is valuable in fields such as anatomy, anthropology, and forensic medicine, contributing to our understanding of evolutionary patterns, species identification, and investigations related to the neck and throat structures. The literature provides valuable insights into various hyoid shapes: H/U, V, B, and D, which were observed in the ranges of 39-55%, 5-48%, 26-48%, and 7-29%, respectively. In a groundbreaking study conducted by Koebke and Saternus in 1979 [20], they meticulously examined a total of 504 hyoid bones, presenting significant findings in the form of shape percentages. The results for H/U, V, B, and D were found as 48.1%, 40.9%, 40.9%, and 11.1%, respectively. This study has since provided valuable insights into the anatomical characteristics of hyoid bones and their respective shape distributions. Comparing our study's findings, we noted a similar occurrence of H/U hyoid shape (20.07%) to that reported by Papadopoulos et al. (38.5%) [19]. Likewise, the frequency of V-shaped hyoid bones in our investigation (11.53%) aligned closely with the findings of Martinez et al. (11.8%) [21], while the proportions of B (15.38%) and D (53.84%) shapes were comparable to those observed by Papadopoulos et al. 26.3% and 28.9%, respectively [19]. As we assessed the hyoid bones based on their symmetric and isometric properties, the symmetric frequency ranged from 52.6% to 93.1%, whereas the isometric frequency was found to be 41%. Generally, other studies [20, 22-24] reported a significantly higher incidence of symmetric hyoid bones, with the exception of Papadopoulos et al.'s findings [19]. Our study revealed a symmetric rate of 34.61%, which closely mirrored Papadopoulos et al.'s results [19]. In regard to the isometric properties, we found a congruence between our study's outcomes and the sole relevant study conducted by Papadopouloos et al. [19].

The Morphometry of Hyoid Bone

In our study, we examined the morphometric characteristics of the height and width parameters of the body of hyoid bones. We observed that our measurements bear the closest resemblance to the findings presented by Kinschuh et al. [18]. In various independent studies, researchers have focused on measuring the major transverse axis distance of the hyoid bone [15, 18, 24] while some other studies taking into consideration the transverse distance between the upper points of the greater horns [15, 22, 25, 26] and the tubercle of the greater horns. In our research, we meticulously measured and recorded all three of these parameters, obtaining mean values of 38.7 mm, 44.19 mm, and 38.81 mm, respectively. Remarkably, our measurements closely resembled the findings reported by Kopuz et al. [24], indicating a notable similarity between the two studies. Regarding the parameter of the anteroposterior vertical length of the hyoid bone, we obtained a mean value of 29.39 mm in our study. This finding is consistent with a study conducted by Kim et al. [15] in 2006 in Korea, indicating a close resemblance between the two investigations. However, our mean value is lower than the one reported by Harjeeth et al. [27] in 1996. Conversely, it is significantly higher than the mean value reported in the study conducted by Kopuz et al. [24] in 2016. The mean value for the length of the body of hyoid bone is recorded as 19.63 mm in our study. This measurement was in close agreement with findings from studies conducted by Miller et al. [26] in the United States in 1998, Martinez et al. [21] in 2008 and Kindschuh et al. [18] in Africa in 2012. However, it was noted to be significantly lower compared to the mean values reported in studies conducted by Kopuz and Ortug [22], Leksan et al. [24] and Harjeet [27]. The angle between the left and right greater horns, as assessed from the superior aspect of the hyoid bone, has garnered attention in studies by Leksan et al. [22] and Kim et al. [15]. In our study, we measured this angle as 40° ± 2.62° in accordance with the measurements reported by Kim et al. [15] and Dursun et al. [28]. However, Leksan et al. [22] have recorded a significantly lower value. Moreover, our study made a notable contribution by introducing new angles associated with the hyoid bone, termed the lateral angle of the greater horn-angulation I and angulation II, which had not been previously explored in the literature. The angulation I and II were measured as 7.52° ± 7.73° and 13.09 ± 3.89, respectively, providing novel insights into hyoid bone morphology. Notably, a remarkable finding was the presence of the lateral angulation (angulation I), which was observed in a total of 59 hyoid bones. Interestingly, there was no prior information available in the literature regarding this angle. However, we came across a case report published by Radunovic et al. [29], in 2018 that presented an angle of 33° between the right greater cornua axis and the hyoid body plane, whereas the left greater horn was found to be in alignment with the hyoid body plane. These unique observations added significant value to our understanding of hyoid bone morphology. The published case report by Radunovic et al. [29] describes a rare anatomical

asymmetry involving the greater horn of the hyoid bone and the superior thyroid horn. The variation could have significant functional implications, potentially affecting swallowing, speech articulation, and respiratory functions. The greater cornua's asymmetry may disrupt the biomechanics of surrounding neck structures, impacting muscle coordination during essential functions. Similarly, asymmetry in the superior thyroid horn may influence the larynx's movement and positioning, potentially affecting voice production and airway protection. Healthcare professionals need to be aware of such variations to consider their functional impact when evaluating and managing patients with speech, swallowing, or respiratory issues. Further research is necessary to fully comprehend the functional significance of this variation. Overall, reporting and documenting such cases contribute to our understanding of human anatomy and guide personalized patient care.

Additionally, our investigation involved a thorough examination of the hyoid bones from the superior aspect, revealing a notable observation. We observed that the endpoints of the greater horns in the bone were not aligned within the same plane. In light of this finding, we measured and recorded the anisometric angle formed between these two horns, quantified at 3.64° ± 1.3°. This novel insight shed light on the unique anatomical variation within the hyoid bone structure. Remarkably, Papadopoulos et al.'s [19] study was the only ones to report on this aspect, revealing that 38 (59%) hyoid bones were classified as an isometric. This finding underscored the importance of understanding the diverse morphological characteristics within the hyoid bone, providing valuable insights for future research in this field.

The study on hyoid bone morphology and morphometric characteristics provides valuable insights, but it has limitations. These include a relatively small sample size, an observational design limiting causal inferences, and a lack of longitudinal data. Selection bias and measurement errors are also possible. It does not extensively explore clinical implications or differences between sexes and age groups. Additionally, a single-center study may introduce institutional-specific factors. Addressing these limitations in future research will enhance the understanding of hyoid bone morphology.

In conclusion, the study focused on examining the morphology and morphometric characteristics of the hyoid bone. Various morphological variations were identified, including U-shaped, boat shape, deviated shape and V-shaped configurations, providing insights into the diversity of the bone across individuals and species. The morphometric analysis measured height and width parameters, aligning closely with previous research and revealing new angles associated with the hyoid bone. A rare anatomical asymmetry involving the greater horn and superior thyroid horn was observed, potentially impacting vital functions. The study highlighted the importance of understanding anatomical variations and their functional implications for personalized patient care. Overall, the research contributes valuable data to the understanding of hyoid bone diversity and complexity in the fields of anatomy, anthropology, and forensic medicine.

Limitations

In previous studies, especially in studies involving dry bones, the demographic information of the cadavers or bones used is not known [30]. Similarly, one of the most important limitations of our study is that more detailed statistical evaluations cannot be made due to the fact that the age and gender of the hyoid bones studied are not known.

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Original Research

Assessment of Extruded Root Canal Filling Materials in Single-Rooted Teeth Using Cone Beam Computed Tomography

Emre Çulha[1], Fatma Tunç[1]

[1] Department of Endodontics, Dental Faculty, Gaziantep University, Gaziantep, Türkiye

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Correspondence
Emre Çulha, DDS, PhD
Address: Department of Endodontics, Dental Faculty, Gaziantep University, Gaziantep, Türkiye
E-mail: emreculha@hotmail.com

ABSTRACT

Objective: Overfilling a root canal has a negative influence on the prognosis of teeth with apical periodontitis. This study proposed to assess extruded sealer and gutta-percha in single-rooted teeth within a Turkish subpopulation using cone-beam computed tomography.

Methods: The study included cone-beam computed tomography scans of 2,346 endodontically treated teeth with a single root and foramen from a private dental clinic's archive. Teeth were divided into four groups: maxillary anteriors, mandibular anteriors, mandibular premolars, and maxillary second premolars. Two endodontists analyzed the scans at all planes and recorded information pertaining to tooth number, tooth type, and presence of extrusion. To examine the data, a chi-square test with a 0.05 p-value was performed.

Results: Extrusion was detected in 256 (10.91%) of the single-rooted teeth. There was significant difference among the groups ($p<0.05$). Extrusion was significantly higher in the maxillary anteriors than in the other tooth groups. Maxillary second premolars had lower extrusion compared to the other tooth groups. There was no statistical relationship between the maxillary anterior tooth groups and the presence of extrusion ($p=0.338$).

Conclusion: Maxillary anteriors had higher root canal filling material extrusion than the other tooth groups, while maxillary second premolars had lower extrusion.

Keywords: Endodontically-treated; Gutta-percha; Overfilling; Root canal filling material; Root canal sealer

INTRODUCTION

One of the cornerstones of endodontic treatment is obturating the root canal space to prevent bacterial infection [1]. In theory, the filling material needs to reach the root's apex without affecting periapical tissues. However, there is no consensus on the apical boundary of obturation. While many researchers base the apical limit on the apical foramen, apical constriction, or cement-dentin-canal junction, others claim that these formations are challenging to identify clinically [2–4]. In the presence of an oval-shaped apical foramen, apical foramina, or lateral canal, the root canal filling material may extrude [3, 5, 6]. Teeth with canal obturations 0–2 mm shorter than the radiographic apex had the highest success rate after endodontic therapy, while underfilled or overfilled canals had much lower success rates [7, 8]. In cases of extrusion, the prognosis is influenced by the filling materials' volume, consistency, solubility in tissue fluids, and biocompatibility [9].

There are controversies in the literature about whether filling a root canal beyond the apex prolongs the periapical healing

process. With adequate endodontic treatment, the great majority of overfilled teeth have been demonstrated to recover successfully [10–12]. Extruded root canal sealer has also been shown to have no negative influence on root canal treatment outcomes [9]. On the other hand, some studies have linked overfilling to unsuccessful root canal therapy [10, 13, 14].

Gutta-percha combined with an appropriate sealer is the most typically utilized root canal filling material. Root canal sealers are toxic to cells and have the potential to harm periradicular tissues. Although it is more biocompatible than root canal sealers [15], extruded gutta-percha may trigger tissue reactions by acting as a foreign body [16]. The relationships between the material's characteristics, the extrusion's location, and the periodontal tissues' immune response can all strongly affect this reaction [17]. Furthermore, a German study reported that extrusion might interfere with the healing process of apical periodontitis [18]. The chemical, cytotoxic, and mechanical effects of extruded canal filling materials have the potential to cause tissue damage to surrounding anatomical structures. Warm filling techniques may also cause thermal damage [19, 20]. In addition, teeth with overfilled canals are likelier to fail than teeth with underfilled canals [21].

Cone-beam computed tomography (CBCT) not only makes it possible to diagnose extruded root fillings but also makes three-dimensional examinations of them possible [22]. This study aimed to use CBCT to assess the presence of extruded sealer and gutta-percha in various kinds of single-rooted teeth in a Turkish subpopulation. The study's null hypothesis was that there was no substantial difference in filling material extrusion among various tooth categories.

Main Points;

- It has been found that the root canal filling material extrusion in maxillary anteriors was higher than other teeth groups and that extrusion in maxillary second premolars was lower than in other single-rooted tooth groups.
- The results from this study to examine the extrusion of filling materials in the root canals of single-rooted teeth can guide studies regarding factors affecting extrusion.

MATERIALS AND METHODS

The study was conducted with the permission of the Clinical Research Ethics Committee of Gaziantep University (Decision Date: 26.10.2022, ID No: 2022/292). The ethical guidelines outlined in the 1964 Declaration of Helsinki and its later revisions, as well as other related ethical guidelines, were followed throughout this investigation. A total of 2,346 teeth with a single root and foramen that had undergone root canal treatment, belonging to the subjects between the ages of 18-93, were included in the study. The study's exclusion criteria included teeth with open apices, root resorption, extensive periodontal disease, periapical pathology, or those that could not be correctly screened due to CBCT aberrations.

All full-size scans with a field volume of 8 × 8 cm and a voxel size of 0.4 mm were taken by Orthophos XG 3D (Sirona Dental System, North Carolina, USA) for different purposes at a private dental clinic. In a darkened environment, a 20-inch LED-backlit screen with 2560 × 1600-pixel resolution was utilized to acquire and display the DICOM (Digital Imaging and Communications in Medicine) images. All planes of the CBCTs were oriented with cursors according to the long axis of each root to analyze the periapical parts. Extruded root canal filling material was defined as canal sealer and gutta-percha that were not restricted to the periodontal ligament. The radiological apex was accepted as the limit for the root canal filling, and the obturation was considered 'overfilled' when there was extrusion of material beyond the radiographic root apex (Fig. 1). Extrusion was also defined as a form that surpassed a semilunar pattern near the radiography apex and was abnormally extended beyond the apex. Two endodontists with more than ten years of CBCT experience simultaneously analyzed the scans using the Sirona Galaxis Galileos Viewer Version 1.9.2 program (Sirona Dental Systems GmbH, Bensheim, Germany) until a consensus was reached.

All personal patient information was anonymized. The data comprises the tooth number and the presence of extrusion. The teeth were divided into four groups: maxillary anteriors (364 central incisors, 314 lateral incisors, and 377 canines; total=1,055), mandibular anteriors (103 central incisors, 114 lateral incisors, and 242 canines; total=459), mandibular premolars (211 first premolars, and 269 2nd premolars; total=480), and maxillary second premolars with one root (total=352). For each tooth, the presence of extruded filling material was recorded regardless of its amount.

Statistical Analysis

The results were evaluated with SPSS V25 software (IBM, Chicago, USA). The study characteristics were determined with standard descriptive methods. To compare categorical demographic characteristics between groups, the chi-square test was performed. A 95% confidence range was used, and $p<0.05$ was considered statistically significant.

RESULTS

Of the 2,346 root-filled teeth examined in the present study, 949 (40.5%) teeth were from males and 1,397 (59.55%) from females. The age distributions of the subjects are as follows; 483 (20.59%) teeth, 18–44 years; 1,084 (46.21%) teeth, 45–64 years; 779 (33.21%) teeth, 65+ years (mean±standard deviation 56.62±13.41; range 19–93). No statistical correlation was found between gender (p=0.742), age group (p=0.168), and the presence of root canal filling extrusion in single-rooted teeth. Extruded filling materials were seen in 256 (10.91%) of the 2,346 endodontically treated single-rooted teeth examined. There was a statistically significant difference within tooth categories ($p<0.05$). Extrusion was present in 13.17% of maxillary anteriors, 11.32% of mandibular anteriors, 5% of maxillary second premolars, and 11.64% of mandibular premolars.

Extruded root canal filling material was mostly found in maxillary anterior teeth, more than in other tooth groups. On the contrary, the percentage of extrusion in maxillary second premolars was the least among all tooth groups (Table 1). Extrusion was observed in 14.6% of maxillary central incisors, 14% of lateral incisors, and 11.1% of canines. There was no statistical relationship between maxillary anterior tooth groups and the presence of extrusion (p=0.338; Table 2).

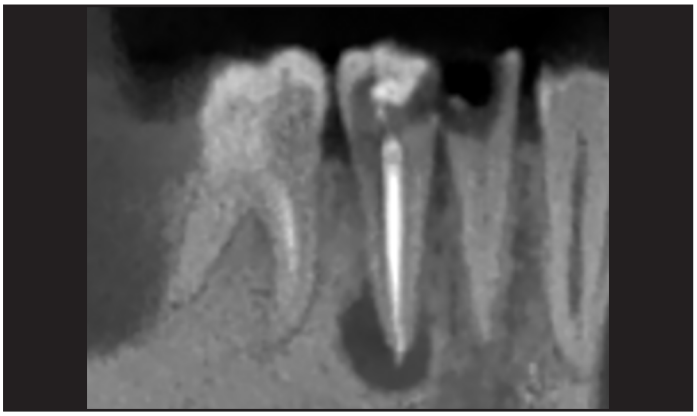

Figure 1. Extrusion of obturation material beyond the radiographic root apex

Table 1. The relationship between tooth groups and the presence of extruded filling material.

Tooth groups	Present N (%)	χ^2	p
Maxillary anteriors	139 (54.3)*	14.484	0.002**
Mandibular anteriors	52 (20.31)#		
Maxillary first premolars	24 (9.38)#		
Mandibular premolars	41 (16.02)#		

Percentages show the distributions within the column.

**p<0.05; chi-square test

*, # Different superscript symbols show statistically significant differences in the same column

Table 2. The relationship between maxillary anterior tooth types and the presence of extruded filling material.

Tooth type	Present N (%)	χ^2	p
Maxillary central incisors	53 (38.13)	2.167	0.338
Maxillary lateral incisors	44 (31.65)		
Maxillary canines	42 (30.22)		

Percentages show the distributions within the column.

chi-square test

DISCUSSION

The most common cause of extruded filling is over-instrumentation. Since the working length of the tooth is not determined correctly, the apical foramen becomes larger than it should be and the apical structure is damaged [23]. Features that affect the formation of the apical barrier, such as complex root canal anatomy, root tip resorption, and immature roots, can often be seen in teeth with overfilling [24, 25]. Due to apical periodontitis, a certain degree of apical root resorption occurs in the teeth. Hence, primary endodontically treated devital teeth and teeth undergoing retreatment are more likely to be extruded than primary endodontically treated vital teeth [9, 24, 26]. Technical problems such as excessive condensation force, hydrostatic pressure, injectable gutta-percha with excessive heat, and the use of a paste carrier during root canal filling processes contribute to extruded root canal fillings [24, 25, 27, 28]. In addition, conditions related to the filling materials, such as excessive fluidity of some sealers and the use of large amounts of sealers and gutta-percha that do not comply with standards, are also factors affecting extruded fillings [25, 27, 28]. No

materials or techniques can completely prevent extrusion [29]. The extrusion rates are 15% with the cold lateral compression technique and between 3–83% with warm vertical compression. This rate can increase to 25–100% using the thermoplasticized gutta-percha technique [27, 30]. The canal-filling technique is a decisive factor in the overfilling of the root canal. Accordingly, the combined application of lateral and vertical condensation techniques significantly increases the probability of overfilling compared with using only a single cone or vertical condensation techniques alone. Furthermore, due to the fluidity created by the compaction techniques applied with heat to the canal-filling material, these techniques are more prone to extrusion [31, 32]. Previous research has classified root filling quality as adequate or inadequate based solely on length [33, 34] or a combination of length and lateral adaptation [35]. A CBCT study in the German population reported an extruded sealer in 8.1% of endodontically treated teeth [36]. Extrusion of all kinds of root-filling material was observed between 1.09% and 31.8% in previous studies [9, 36–41]. Although it is difficult to distinguish gutta-percha from root canal sealer radiographically, studies examining sealer extrusion reported a prevalence of 6.9–8.12% of teeth with extrusion [36, 42]. In the current study, 13.17% of maxillary anteriors with root canal treatment had an extrusion. This rate was similar to studies using CBCT (12.3% and 13.95%) [36, 42], but higher than studies evaluating extrusion with periapical radiography, which ranged from 1.17–5.14% [43, 44]. The percentage of teeth with extrusion (16% and 17.75%) found in two studies evaluating maxillary anterior root canal treatments by dental students, were higher than in the current study [43, 45]. These high results might have occurred due to inexperienced operators.

In our study, extrusion in maxillary second premolars (6.81%) was higher than the only study in the literature (3.75%) in which the maxillary second premolars were evaluated separately [36]. Also, our findings showed extrusion in 11.32% of endodontically treated mandibular anteriors, which was similar to studies using CBCT ranging from 10.5–11.11% [39, 46]. A study focusing on dental students in Türkiye reported that 19.26% of mandibular anteriors had a root canal filling extrusion [45]. However, this rate was higher than in studies using periapical radiography (0–2.63%) [43, 44]. In the current study, 8.54% of root canal filling material extrusion observed in mandibular premolars was similar to that of a German and a Turkish study [36, 45], but higher than other studies [39, 43–45]. When evaluating the maxillary and mandibular anterior teeth together, there was an extrusion in the range of 13–18.13% [38, 41]. Although these studies used periapical radiography, their results were close to the current study (12.61%). Similarly, in some studies where all maxillary and mandibular premolars were evaluated together, extrusion was reported between 4.59% and 23% [38, 40, 41, 43, 45]. The fact that these studies did not distinguish between root and canal counts when obtaining information can be used to explain the large variation in percentage.

Extrusion in maxillary anterior teeth was significantly higher than in other tooth groups. Since these teeth have larger canal diameters, more gutta-percha and canal sealer might be used in the obturation procedure. Moreover, it is easier to physically reach this group of teeth clinically and to perform vertical condensation. These factors might have increased the possibility of extrusion. From the same perspective, the incidence of extrusion in maxillary second premolars was statistically lower than in other tooth groups. The fact that the maxillary second premolars are located more posteriorly in the oral cavity and are more difficult to reach clinically than the other tooth groups in the study, this might have prevented the use of excessive force during root canal filling. Some studies report that the extrusion of root canal sealers is more likely to occur in premolars [47]. Conversely, a randomized clinical experiment reported the occurrence of extruded canal filling material in anterior teeth to be greater than in premolars, similar to our findings [48]. In the same study, it was shown that anterior teeth and premolars cause more overfilling than molars, which might be because anteriors and premolars have flatter and larger root canal morphologies compared with molars. However, it has been determined that tooth type loses its importance as a determining factor in canal filling material extrusion [48].

Limitations

The first limitation was the possibility for the extruded root canal filling materials that were histologically detectable, but too resorbed to distinguish be by CBCT imaging [9]. The second limitation is that CBCT images of teeth after primary or secondary endodontic treatments were not evaluated in the present study. In addition, it was not recorded whether the teeth were vital or devital before the endodontic procedure or filling technique used in the root canal. A further limitation of the present study was the use of the radiographic apex rather than the apical constriction in determining the existence of extrusion. As a final limitation, it was difficult to distinguish gutta-percha from root canal sealers when assessing overfilling

using CBCT images. In previous studies that have experienced this challenge, “overfilled”, “overextended”, “over apex”, “long filling”, and “inadequate obturation” have been used to describe extruding root canal filling material, regardless of gutta-percha or root canal sealers [9, 36–41]. There was only one study that specifically used the term “sealer puff” for the extrusion of root canal sealers [36].

CONCLUSIONS

The current study indicated that the root canal filling material extrusion in maxillary anteriors was higher than in other tooth groups, whereas the extrusion in maxillary second premolars was lower than in other tooth groups. There was no statistical relationship between maxillary anterior tooth groups and the presence of extrusion. In further studies, factors affecting extrusion such as filling technique, filling material, and apical condition should be examined separately, not only in single-rooted teeth, but also in multi-rooted teeth. Dentists should be more careful to avoid extrusion when filling the root canals of single-rooted teeth, especially the maxillary incisors and canine teeth.

Conflict of interest: The authors declare no conflicts of interest.

Informed Consent: Informed consent was obtained from patients participating in the study.

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Ethical Approval: The study was conducted with the permission of the Clinical Research Ethics Committee of Gaziantep University (Decision Date: 26.10.2022, Approval No: 2022/292).

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Original Research

Effects of Pinealectomy and Melatonin Application on Serum Melatonin, Nesfatin-1 and Ghrelin Levels

Saadet Sonmez[1], Esma Menevse[2], Saltuk Bugra Baltaci[3], Omer Unal[4], Rasim Mogulkoc[1], Abdulkerim Kasim Baltaci[1]

[1] Faculty of Medicine, Department of Physiology, Selçuk University, Konya, Turkey
[2] Faculty of Medicine, Department of Biochemistry, Selçuk University, Konya, Turkey
[3] Department of Physiology, Regenerative and Restorative Medical Research Center, Istanbul Medipol University, Istanbul, Turkey
[4] Kırıkkale University, Medical Faculty, Department of Physiology, Kırıkkale, Turkey

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Correspondence
Abdulkerim Kasim Baltaci
Address: Selcuk University, Medical Faculty, Department of Physiology, Konya / Turkey
E-mail: baltaci61@yahoo.com

ABSTRACT

Objective: In this study, it was aimed to investigate the relationship between the pineal gland and ghrelin and nesfatin-1 hormones in rats.

Methods: A total of 36 male rats were used in the study, and the animals were divided into 4 groups. Group 1, Control; Group 2, Pinealectomy (Px); Group 3, Px+Melatonin; Group 4 Melatonin. After the end of the experimental applications, melatonin, ghrelin and nesfatin-1 levels (ELISA) were determined in the blood samples taken from the animals.

Results: While pinealectomy resulted in suppression of melatonin levels, melatonin supplementation led to a significant increase in blood melatonin levels ($p<0.01$). Melatonin supplementation suppressed ghrelin levels, while pinealectomy increased ghrelin levels ($P<0.01$). On the other hand, Nesfatin-1 levels, which increased with melatonin support, were significantly suppressed by pinealectomy ($p<0.01$).

Conclusion: The findings of the study draw attention to an important relationship between the endocrine activity of the pineal gland and the hormones ghrelin and nesfatin-1, which play a critical role in nutrition. Consequently, administration of melatonin inhibits ghrelin but increases nesfatin-1.

Keywords: Pinealectomy, melatonin, nutrition, nesfatin-1, ghrelin, rat.

INTRODUCTION

The properties of the Nesfatin-1 molecule as a hormone were revealed in 2006. This molecule secreted from the hypothalamus has also attracted the attention of researchers with its role in the regulation of nutrition [1]. The suppressive effect of food intake by Nesfatin-1 is independent of leptin. The effect of Nesfatin-1 occurs only through a melanocortin receptor-dependent mechanism [2,3]. The precursor of this molecule is NUCB2 (pronesfatin), an 82 amino acid peptide that suppresses food intake. Compounds such as precursor protein (NUCB2), nucleobindin-2 (pronesfatin), prohormone converters pronesfatin nesfatin-1 (amino acids 1-82), nesfatin-2 (amino acids 85-163) and nesfatin-3 (amino acids 166-396) occurs [1-4]. Conversion of the NUCB2 molecule to nesfatin-1 is required for the suppressive effect of food intake to occur. [1]. Consequently, Nesfatin-1 is an amino terminal fragment derived from NUCB2. Its amount in the hypothalamic nucleus decreases in starvation. [1]. Therefore, its role in feeding behavior is important.

Ghrelin hormone is produced in the neuroendocrine cells in the fundus and pylorus regions of the stomach where ghrelin is mainly released [5]. Concentration of ghrelin peptide shows about 65% decrease in rats which are subjected to gastrectomy. It is known that in the regulation of ghrelin secretion in the stomach, besides the factors affecting nutrition, hormonal factors are also effective [6]. The ghrelin hormone is not only limited to the digestive system, it is also released in the stomach veins and participates in the general circulation. It has been shown that the hormone ghrelin can cross the blood-brain barrier and affect hypothalamus functions [7]. The hormone ghrelin, which crosses the blood-brain barrier, affects the hypothalamus functions in both humans and some rodents and contributes to the regulation of feeding [8,9]. It has been reported that central and peripheral administration of the hormone ghrelin may increase appetite, leading to increased food intake and consequent obesity in rodents [10]).

Ghrelin, which plays a role in feeding behaviors, is a hormone that increases appetite. Therefore, it is defined as orexigenic hormone [11,12]. The ghrelin hormone secreted from the stomach is carried to the brain through the blood. It is also referred to as a brain-intestinal peptide because it has an appetite-increasing effect in the hypothalamus [13]. This hormone exerts its appetite-increasing effect through the molecule Neuropeptide-Y (NPY), which is a strong stimulant of nutrition in the hypothalamus [14].

There is no consensus on the effect of melatonin (MT) on feeding behaviors. It has been shown that the food intake-enhancing effect of melatonin administration in rats is evident in medium and low dose applications. [15]. This shows that melatonin supplementation in nutritional behaviors may be dose dependent. It has been reported that melatonin does not have a direct effect on food intake, but may have an indirect hyperphagic effect because it suppresses 5-HT2A [16]. In conclusion, melatonin is a hormone associated with feeding behaviors.

Main Points;

- The results of the current study show that the pineal gland may have important effects on the hormones ghrelin and nesfatin-1, which play critical roles in nutrition.
- In conclusion melatonin supplementation inhibites ghrelin, and but increases nesfatin-1.

Studies about on relation between melatonin and nesfatin-1 are very few in the literature. Studies conducted with some animal species such as frog and fish have shown a possible relationship between nesfatin-1 which plays an important role in the regulation of nutrition and pineal gland [17]. It has been emphasized that melatonin administration causes an increase in gastric ghrelin release in rats [18], and there may be a significant association between pineal gland and ghrelin [19, 20]. Orexigenic effect of ghrelin which is an important hormone in the stimulation of nutrition occurs via NPY. The relationship between Ghrelin hormone which has an important critical effect on NPY and pineal gland is yet to be understood.

The objective of this study was to determine how nesfatin-1 and Ghrelin hormone influenced in rats subjected pinealectomy and melatonin supplementation.

MATERIALS AND METHODS

Experimental procedures of the present study were carried out at Selcuk University Experimental Medicine Research and Application Center. The study protocol was approved by the experimental animal ethics committee of the same center (no: 2015-87).

In the study performed on 36 adult male rats, the animals were divided into 4 groups. While the control group consisted of 6 rats, the administration groups consisted of 10 rats.

Group 1: Control: Animals in this group were not treated.

Group 2: Pinealectomy (Px): The rats in this group underwent pinealectomy under general anesthesia.

Group 3: Px + Melatonin: Rats underwent pinealectomy under general anesthesia and subcutaneous melatonin (5 mg/kg/day) was administered for 1 month after pinealectomy.

Group 4: Melatonin: The rats in this group were given subcutaneous melatonin (5 mg/kg/day melatonin for 4 weeks).

Experimental Procesures

Melatonin Administration

Melatonin was commercially supplied (Sigma M-5250). Melatonin was subcutaneously injected to the rats with a dose of 5 mg/Kg/day at A.M. 10:00. Melatonin injections were carried out at the same hours for 28 days.

Pinealectomy Application

Pinealectomy procedure was performed in rats under general anesthesia. Anesthesia was induced with 60 mg/kg ketamine hydrochloride (Ketalar, Parke – Davis) and 5 mg/ kg xylazine (Rompun, Bayer). Pinealectomy procedure was applied following the method described by Kuszack and Rodin [21].

Blood Collection

After the completion of the experimental stages of the study, all animals were sacrificed under general anesthesia and serum samples were taken. General anesthesia was administered to all animals (with intramuscular administration of a combination of Ketalar (60 mg/kg), Parke-Davis and xylazine (5 mg/kg) "Rompun, Bayer") to avoid animal suffering.

Biochemical Procedures

Melatonin Analysis

Melatonin analysis was carried out using Cusabio Melatonin ELISA test kit (Catalog no: CSB-E13433r). The samples were read at 450 nm with BMG-LABTECH brand SPECTRO start Nano ELICA device (Germany). The results were given as pg/ mL.

Ghrelin Analysis

Ghrelin analysis was performed using Cusabio Rat ELISA test kit (Catalog no: CSB-E9816r). The samples were read at 450 nm with BMG-LABTECH brand SPECTRO start Nano ELICA device (Germany). The results were determined as ng/mL.

Nesfatin-1 Analysis

Nesfatin1 analysis was performed using Cusabio Rat ELISA test kit (Catalog no: CSB-E14378r). The samples were read at 450 nm with BMG-LABTECH brand SPECTRO start Nano ELICA device (Germany). The results were given as ng/mL.

Statistical Analysis

Statistical evaluation of the results was made with SPSS 22.0 statistical software, and arithmetic means and standard deviations were determined. Homogeneity of the data was examined with Shapiro-Wilk test, and the data were found to non-normally distribution. Kruskal-Wallis H test was used in determination of the differences between the groups, and Mann-Whitney U test was utilized to found the group causing difference. P<0.01 values were considered statistically significant.

RESULTS

Comparison of Serum Melatonin Levels Among the Groups

Group 2 has the lower melatonin than other all groups (p<0.01). Serum melatonin levels were higher in the pinealectomy + melatonin supplementation (Group 3) compared to the control (Group 1) and pinealectomy (Group 2) groups (p<0.01). In our study, the highest serum melatonin levels were found in the melatonin group (Group 4) (p<0.01) (Figures 1).

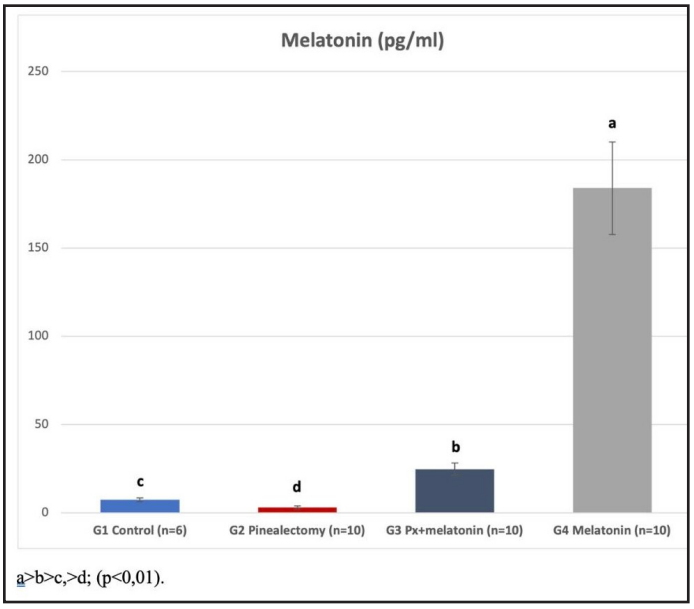

Figure 1. Serum Melatonin Levels of Study Groups

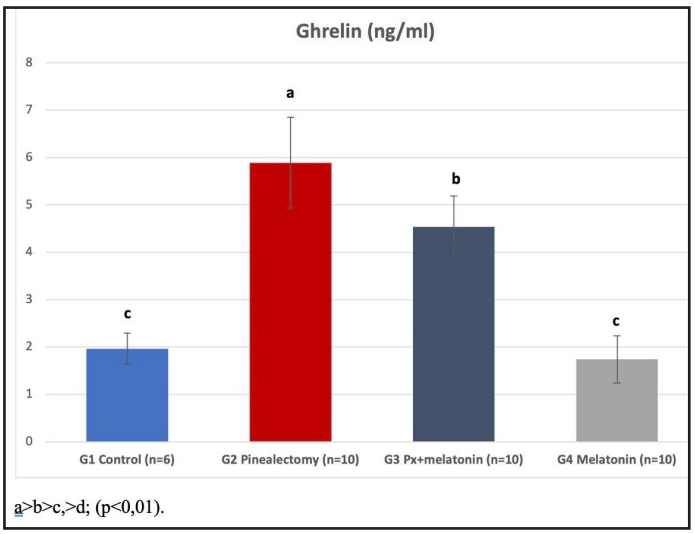

Figure 2. Serum Ghrelin Levels of Study Groups

Comparison of Serum Ghrelin Levels Among the Groups

Lowest serum ghrelin levels were obtained in Group 1 (control) and Group 4 (melatonin group) (P<0.01). Serum ghrelin levels of

Px+melatonin group (Group 3) were higher compared to Groups 1 and 4 (P<0.01), and lower compared to Group 2 (Px group) (P<0.01). The highest serum ghrelin levels were found in the Px group (Group 2) (P<0.01, Figures 2).

Comparison of Serum Nesfatin-1 Levels Among the Groups

Pinealectomy group has the lowest Nesfatin-1 (Group 2) (P<0.01). Nesfatin-1 levels of the Px+melatonin group (Group 3) were higher than that of the control and Px+melatonin groups (P<0.01). The highest serum Nesfatin-1 levels were observed in the melatonin supplementation (Group 4) (P<0.01, Figures 3).

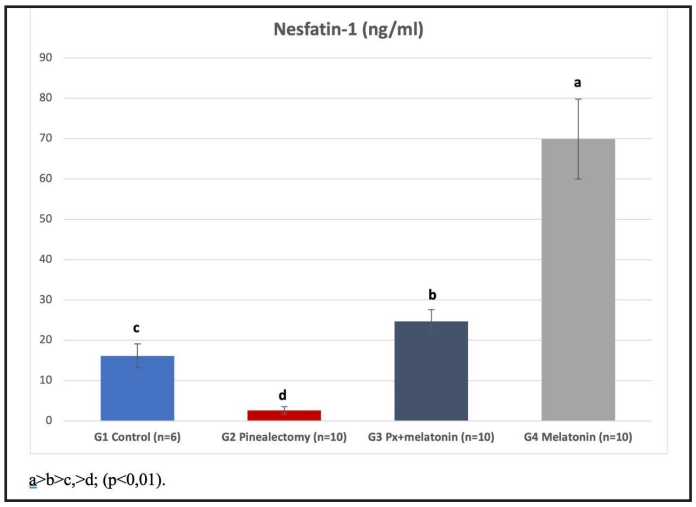

Figure 3. Serum Nesfatin-1 Levels of Study Groups

DISCUSSION

Discussion of Melatonin Results

Pineal gland is the main source of the synthesis and release of melatonin hormone. However, besides pineal gland melatonin synthesis occurs also in "digestive system, respiratory system, kidneys, adrenal glands, structures related to cellular immunity, thyroid gland and placenta" [22, 23]. For this reason, despite decreased melatonin levels in the animals which pineal gland is removed, there are measurable levels of melatonin hormone in the circulation. [23]. In our study, the lowest melatonin levels were obtained in Group 2, which underwent pinealectomy, and the highest melatonin levels were obtained in the groups that received melatonin (G3, G4). Our results regarding melatonin levels show that pinealectomy in animals was successful in this study [23, 24]. This will also enable a more credible discussion of our other results.

Discussion of Ghrelin Results

Results of the studies investigating relationship of the pineal gland and its product melatonin with nutritional behaviour are controversial. Some reports have shown that melatonin affects food intake, fat deposition and body weight in mammals [25]. Melatonin has been reported to cause decreases in fat mass and body weight in Siberian hamster [26] and rats [27]. In contrary, melatonin has been reported to increase fat mass in Syrian hamsters [28] and body weight in racoons [29]. On the other hand, Mustonen et al., [30] determined no any change in body weight after melatonin therapy. However, it is obvious that melatonin plays a role in nutritional behaviour [31]. In the present study, the highest serum Ghrelin levels were determined in Px group (Group 2), and the lowest levels in the control (Group 1) and melatonin (Group 4) groups. Serum ghrelin levels of the Px+melatonin group (Group 3) were higher compared to Groups 1 and 4, and lower compared to the Px group (Group 2). In their study on fish, De Pedro et al. [25] found that chronic melatonin administration creates a tendency to suppression of circulating ghrelin levels. It has been reported that supplementation of the amino acid tryptophan, a precursor in melatonin synthesis, at a dose of 1 g for 5 days increased food intake in dogs but did not change ghrelin levels [32]. Raised ghrelin levels in starvation have been shown to decrease after administration of oral melatonin or tryptophan amino acid both in patients with liver cirrhosis and healthy control persons [33]. Results of the limited number of above mentioned studies indicate to a relationship between melatonin and ghrelin. In our study, increased ghrelin levels were obtained in the pinealectomized rats, while melatonin application in the pinealectomized rats rats significantly decreased ghrelin levels compared to the pinealectomy group. However, ghrelin levels of the px+melatonin group were higher than the controls. A study by Mustonen et al. [20] reporting decreased plasma ghrelin levels with exogenous melatonin application in rats supports our finding that increased ghrelin levels in the pinealectomy group were reduced with melatonin administration. At least it can be said related to our results that, there is an important correlation between pineal gland and ghrelin levels. Removal of the pineal gland results in change also in ghrelin release. Comparing with the studies examining the relationship between melatonin administration and ghrelin, studies investigating the relationship between pinealectomy and ghrelin are quite limited. In their study, Canpolat et al. [16] reported that removal of the pineal gland had no effect on gastric ghrelin, but pinealectomy may significantly influence ghrelin responses in the hypothalamus. Based on this finding, the same authors proposed that pineal gland may be crucial in ghrelin responses in the hypothalamus [16]. A similar result

was reported by Aydin et al. [34]. Results of the ghrelin levels we obtained in this study are partially consistent with above mentioned studies. The number of publications which we could discuss our results one-to-one in all dimensions is quite limited. However, it was found related to our ghrelin results that pinealectomy leads to significant increase in ghrelin levels in rats, and although exogenous melatonin application cause to a decrease in ghrelin levels, this decrease did not reach to the levels of the control subjects. Exogenous melatonin induced anorectic properties, and reduces the expression of ghrelin [35]. Interestingly, no any change was observed in the ghrelin levels of the rats given exogenous melatonin without subjected to pinealectomy compared to the animals in the control group. Based on this result, it can be said that presence of the pineal gland is functionally needed in the regulation of serum ghrelin levels

Discussion of Nesfatin-1 Results

Present study indicated that Nesfatin-1 levels were lowest in pinealectomy group. Nesfatin-1 levels of the Px+melatonin (Group 3) were higher compared to the control and Px+melatonin groups. The highest serum Nesfatin-1 levels were observed in the melatonin supplementation. Nesfatin-1 can be considered as a newly defined peptide. The most important interesting effect of Nesfatin-1 is its leptin independent food intake suppressing effect [36]. Nesfatin-1 which has been reported as the satiety molecule in the hypothalamus and cerebrospinal fluid [1], has also been reported to be found in diffrent hypothalamic nucleus such as the ARC, PVN, SON and lateral hypothalamic area [1] in various organisms. Various experiments have supported inhibitory role of Nesfatin-1 on food intake [1, 36] and indicated that it may have glucose regulatory effect in diabetic mice [36]. The mentioned studies have demonstrated that Nesfatin-1 may also play a role in the regulation of metabolism. Interestingly; nesfatin-1 like reactivity has been found in the pineal gland of frogs [17], that suggest a potential relationship between the pineal gland and its product melatonin, and nesfatin-1. Nesfatin -1 is known to decrease nocturnal feed intake in rats, and at the same time it has been suggested that serotonin may also have a role in appetite suppressing effects of Nesfatin-1 [37]. Melatonin synthesized by serotonin and the presence of a high-level rhythmic secretion at night [23], is similar to the findings of the study by Stengel ve Taché. Many study have proposed that melatonin is effective on nutritional behaviour, and this effect especially occurs via leptin which suppresses appetite [23,31,38]. We could not found a study in Med-line screening to compare our results one-to-one. There is no any study drawing attention to the relationship between melatonin and nesfatin-1 except for the study by Senejani et al. [17] which was conducted on frogs and emphasized the potential association between the pineal gland and nesfatin-1. Previous study showed that some central regulators are important in different metabolism such as controlling proliferation and function. These regulators are neuropeptide Y (NPY), cocaine- and amphetamine-regulated transcript (CART), melatonin and leptin. In our study, CART has not been investigated but it has a relationship pineal gland. In future studies, this relationship may be investigated in much more detail [39].

In the present study; we found significant suppression in nesfatin-1 levels in the pinealectomized rats, and obtained increased nesfatin-1 levels with melatonin supplement in the pinealectomized rats compared to the control animals. However, more interestingly we obtained the highest nesfatin-1 levels in the group which we administered melatonin. We think that this result in our study is the first in the literature.

Based on the results we obtained from this study, it can be said that pineal gland is needed in the regulation of ghrelin and nesfatin-1 levels, thus their functions, and even pineal gland may play an important role in nutritional behaviour of the mentioned hormones.

Limitations

The limiting factor in the current study is that the relationship between the pineal gland and ghrelin and nesfatin-1 was not demonstrated with various melatonin doses and administration times. Elimination of this gap in future studies may enable us to access new and critical information.

CONCLUSION

Our findings show that;

1.Pinealectomy leads to a significant increased ghrelin which is a stimulator of food intake.

2.Melatonin administration reverses this increase in the pinealectomized rats.

3.Again in this study, we obtained significant suppression in nesfatin-1 in rats, and increased nesfatin-1 with melatonin supplement in the pinealectomized rats compared to the control animals.

4.However, more importantly we obtained the highest nesfatin-1 levels in melatonin alone group.

5.According to the results obtained in the present study, endocrine activity of the pineal gland plays a critical role in the regulation of ghrelin and nesfatin-1 levels and thus their functions.

Research Data Policy and Data Availability Statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Compliance with Ethical Standards: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Experimental Animals Ethics Board of Selcuk University Experimental Medicine Research and Application Center (2015-87). This research was performed on the animals (rat).

Conflict of Interest: The authors declare that they have no potential conficts of interest to disclose.

Author Contributions: SS, EM, SBB and OU made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; SBB, RM and AKB drafted the work or revised it critically for important intellectual content, approved the version to be published. The authors declare that all data were generated in-house and that no paper mill was used.

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Original Research

Readability and Quality Assessment of Web-Based Information Concerning Post-Endodontic Treatment Selection

Gülbahar Erdinç[1], Olcay Özdemir[2]

[1] Department of Prosthodontics, Karabük University, Faculty of Dentistry, Karabük, Türkiye
[2] Department of Endodontics, Karabük University, Faculty of Dentistry, Karabük, Türkiye

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Correspondence
Gülbahar Erdinç, MD
Address: Department of Prosthodontics Faculty of Dentistry Karabük University, Demir Çelik Campus, Karabük, Türkiye
E-mail: gbaharerdinc@gmail.com

ABSTRACT

Objectives: This study aimed to unbiasedly identify the quality and readability of the written information about post-endodontic coronal restorations on Turkish websites using accepted formulas and scales by the literature.

Methods: The study was carried out by setting national pages and national locations in the Google search engine. The terms "root canal treatment and veneer" and "root canal treatment and filling" were used as keywords. The webpages were assessed independently by two readability formulas (Flesh-Kincaid and Ateşman systems) and DISCERN quality kit. The independent statistical and correlation analysis were performed using Kolmogorov-Smirnov, Shapiro-Wilk, Spearman's rho, and Dunn's tests. The significance level was taken as $p<0.05$.

Results: The initial search identified 60 websites, of which eight were excluded due to non-compliance with the study criteria (n=52). According to the DISCERN score, the web pages were categorized as fair with the highest rate of 57.69%. A statistically significant positive correlation was found between Ateşman Readability Index and the Flesh-Kincaid Reading Ease score ($r=0.998$; $p<0.001$). There was no statistically significant correlation between Ateşman Readability Index and DISCERN score ($p=0.259$). Ateşman reading ease scores of the web pages are evaluated, 80.76% of these are classified as moderately difficult.

Conclusions: The readability distribution of the written information about post-endodontic coronal restorations on websites was acceptable to the majority. However, being readable does not indicate that it provides sufficient target technical information. In this context, it can be suggested to use readability and quality scales while preparing websites for dental patient education concerning post-endodontic coronal restorations.

Keywords: Patient education, Readability, Postendodontic restoration, DISCERN, Access to information

INTRODUCTION

Technological and digital developments provide to attain needed information from anywhere and anytime. Web-based pages can be used to access knowledge on many subjects, including health-related issues [1]. The rate of searching for health-related information is very high compared to others and the most common purpose of Internet use among the others [2,3]. However, there is no mechanism to check the accuracy of health-related information on the websites. The difficulties of accessing accurate and reliable information on websites have been mentioned in previous studies [4,5].

Readability is generally defined as the ease of comprehension or understanding because of writing style. Objectively evaluating the readability of the text is essential to make this distinction [5]. Various readability evaluation formulas have been developed to assess a text's readability [6-8]. In the 1940s, Rudolph Flesch, developed the Flesh-Kincaid system based upon a formula that incorporates formula average sentence length and the average number of syllables per word [9]. Ateşman et al. developed a scale to evaluate the readability of Turkish texts in 1997 and reported that readability only gives information about the style of the text, not about the quality of the technical information of the text [10]. Besides, Charnock et al. developed the DISCERN tool kit in 1999, enabling information providers and patients to judge the quality of information on websites about dental and medical treatment options [11]. This kit is intended to assist patients in evaluating all aspects of their dental or medical treatment [12].

Various treatment options have been described in the literature, such as filling, veneer, inlay, onlay, overlay, post-core restorations, and recently CAD-CAM systems and endocrowns which can be applied to the endodontically treated tooth [13,14]. However post-endodontic treatment options are still a dilemma for clinicians and patients. There are always burning questions such as: "Is root canal treatment the only approach to treating the tooth? What is the difference between filling and root canal filling? Will it be finished after the root filling? Is it possible to do only restoration for this tooth or is it possible to do only root canal treatment for this tooth?" It is possible to multiply these kinds of questions. The treatment of a tooth is holistic from the patient's point of view but may have different stages that may concern other clinical disciplines and sure it is a must to explain all treatment steps and options to patients using evidence-based dentistry before starting the management.

Main Points;

- Nowadays, it is essential that this information is at a level that patients can understand, as patients often try to get preliminary information from online sources before reaching the physician.
- Root canal treatment and coronal restoration are inseparable, and both should be included in the information.
- According to the DISCERN score, the web pages were categorized as fair, with the highest rate of 57.69%.
- Ateşman reading ease scores of the web pages are evaluated, 80.76% of these are classified as moderately difficult.

It is predictable to want to get an idea about disease or complaints, also, it is possible to search treatment options and risks; therefore Internet is generally used as a tool for research [5]. Especially in the health field, many web pages have shared information on the issues that patients are highly curious [5,15]. In this context, the aim of this study was to unbiasedly evaluate the quality and readability of the written information about both root canal treatment and possible subsequent coronal restorations on Turkish websites using accepted formulas by the literature.

MATERILS AND METHODS

The readability and quality of the information related to the research topic were evaluated on websites open to the public and accessible to everyone in the present study. Since legal regulations consider that research using publicly available data does not involve human subjects, this protocol did not require ethics committee approval. The study was carried out by setting Turkish pages and Türkiye locations in the Google search engine. The terms "root canal treatment and veneer" and "root canal treatment and filling" were used as keywords in the search engine, and the search was performed on September 3, 2022, by a single researcher using the same computer. After searching for each keyword, the first 30 websites were evaluated. Duplicate pages, links to research studies, advertisements, pages that require membership, pages that require acceptance of cookie settings, and websites that share information only with video instead of written text and do not contain information about all keywords were excluded from the study. Two examiners independently evaluated websites meeting the inclusion criteria (n=52). The source of each web page was classified as private clinics and university hospitals.

Independently, two examiners assessed all web pages included in the study. Regarding both scales, when a divergent judgment was observed between the examiners, the page was re-assessed to the achievement of a consensus score. To evaluate the quality of all websites included in the study and to report unbiased results, a prosthodontist and an endodontist read the texts on all websites. DISCERN instrument was used for the quality assessment. The 16 questions in the DISCERN tool kit were scored and recorded over 1-5 points, with a consensus between the two researchers. The results obtained were calculated as

mean scores, percentages, and ranges. DISCERN consists of 16 questions, each scored between 1 and 5 according to the completeness of the evaluated information (Table 1). The first to the eighth question addresses the publication's reliability, and questions 9-15 address specific details for treatment options; the last question is a summary question for overall rating. Section 1 consists of eight questions to evaluate the publication's reliability, and section 2 consists of seven questions to analyze the quality of treatment choices. The website's overall quality is assessed in Section 3 with one question. The websites were categorized as by the total DISCERN score, except last question: 15-75; 15-26: very poor, 27-38: poor, 39-50: average, 51-62: good, and 63-75: excellent.

Table 1. The DISCERN Instrument

Section	Question
1	Are the aims clear?
	Does it achieve its aims?
	Is it relevant?
	Is it clear what sources of information were used to compile the publication (other than the author or producer)?
	Is it clear when the information used or reported in the publication was produced?
	Is it balanced and unbiased?
	Does it provide details of additional sources of support and information?
	Does it refer to areas of uncertainty?
2	Does it describe how each treatment works?
	Does it describe the benefits of each treatment?
	Does it describe the risks of each treatment?
	Does it describe what would happen if no treatment is used?
	Does it describe how the treatment choices affect overall quality of life?
	Is it clear that there may be more than one possible treatment choice?
	Does it provide support for shared decision-making?
3	Based on the answers to all of the above questions, rate the overall quality of the publication as a source of information about treatment choices

To evaluate the readability of the studies, the word count, sentence count, word length, sentence length, and readability index of the texts presented on the websites were calculated using a free automatic online calculator (www.okunabilirlikendeksi.com). The readability level of each website was computed using the Ateşman readability formula, which is widely used for Turkish texts. At the same time, the readability level of the web pages was classified according to the ranges that rated the readability formulas for reading ease. In addition, the online method used in calculating the readability index was verified manually using the formula below.

Ateşman readability formula = 198.825 – 40.175 × (total syllables / total words) – 2.610 × (total words / total sentences)

The Flesch-Kincaid Grade Level (FKGL) is a standard metric used to evaluate the grade of the complexity of English texts. The FKGL scores equal the US grade level of education that the reader needs to understand. Although Turkish texts were evaluated in this study, based on the use of this formula in different languages in previous studies, an additional evaluation was made using this formula.

FKGL formula = 0.39 × (words / sentences) + 11.8 × (syllables / words) − 15.59

Reading ease score and descriptive categories were evaluated for both readability formulas. The scores range between 1 and 100, with higher scores deemed easier to read. The scores and classes of Ateşman are 90-100: very easy, 70-79: easy, 50-69: moderately difficult, 30-49: difficult, and 1-29: very difficult. The scores and categories of Flesch are 90-100: very easy, 80-90: easy, 70-80: fairly easy, 60-70: standard, 50-60: fairly difficult, 30-50: difficult, 0-30: very difficult.

Data were analyzed with IBM SPSS V23. Conformity to normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. The relationship between normally distributed scores was analyzed using the Pearson correlation coefficient. The relationship between non-normally distributed scores was analyzed using Spearman's rho correlation coefficient. One-way analysis of variance was used to compare normally distributed data according to groups of three or more, and multiple comparisons were examined with Duncan's test. The Kruskall-Wallis H test was used to compare data that were not normally distributed according to groups of three or more, and multiple comparisons were examined with Dunn's test. Analysis results were presented as mean ± standard deviation and median (minimum–maximum) for quantitative data. The significance level was taken as $p<0.05$.

RESULTS

The initial search identified 60 websites, of which 8 were

excluded due to non-compliance with the study criteria. The remaining 52 web pages were assessed, and while only 3 were the pages of university hospitals, all the rest were web pages of private clinics.

Statistical analyzes according to sections and total DISCERN score are given in Table 2. Good and excellent categories were not included in the analysis because the number of observations was insufficient and statistical comparison was meaningless. A statistically significant difference was found between Section 1 mean values according to DISCERN levels ($p<0.001$). This difference was observed between all groups. A statistically significant difference was found between the median values of Section 2 according to DISCERN levels ($p<0.001$). This difference was observed between very poor and poor levels and fair levels. A statistically significant difference was found between the median values of Section 3 according to DISCERN levels ($p<0.001$). This difference was observed between very poor and poor groups and fair grades. A statistically significant difference was found between the median values of DISCERN score according to DISCERN levels ($p<0.001$). This difference was observed between very poor and poor groups and fair grades.

Table 2. Comparison of Section 1-2-3 according to Discern levels

	Very Poor	Poor	Fair	p
Section 1	14.5 ± 2.08[a]	17.88 ± 1.93[b]	21.8 ± 2.14[c]	**<0.001[c]**
	14.5 (12 - 17)	17.5 (15 - 22)	22 (18 - 28)	
Section 2	7.75 ± 0.96	11.31 ± 2.47	19.37 ± 2.43	**<0.001[d]**
	7.5 (7 - 9)[b]	10 (9 - 17)[b]	19,5 (16 - 23)[a]	
Section 3	1.75 ± 0.5	2.13 ± 0.34	3.4 ± 0.5	**<0.001[d]**
	2 (1 - 2)[b]	2 (2 - 3)[b]	3 (3 - 4)[a]	
Discern	24 ± 1.63	31.31 ± 3.07	44.57 ± 3.88	**<0.001[d]**
	24 (22 - 26)[b]	31 (27 - 38)[b]	44,5 (39 - 50)[a]	

a-b: There is no difference between levels with the same letter (Duncan test, Dunn test).
[c] One-way analysis of variance,
[d] Kruskal Wallis H test, mean ± s. deviation, median (min–max)

According to the total DISCERN score and categories, the distribution between the number of web pages is shown in Figure 1. Only two web pages were evaluated as good, no web pages were specified at the excellent level, and the web pages were categorized as fair with the highest rate of 57.69%.

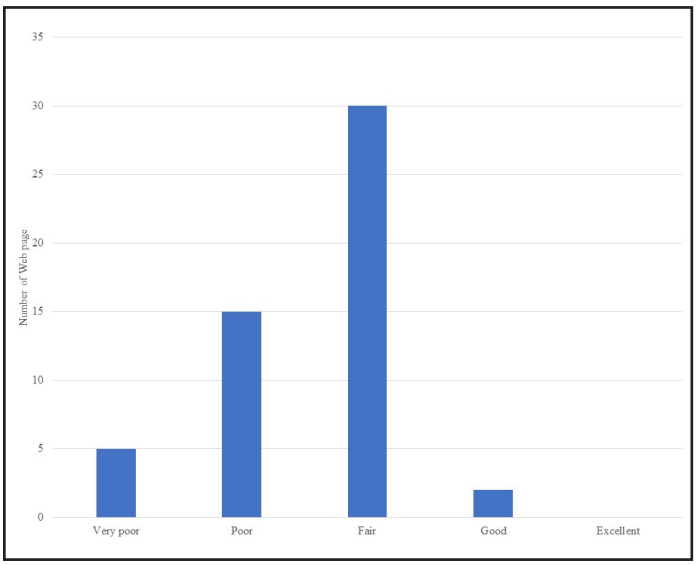

Figure 1. Number of web pages according to the total DISCERN score and categories

A statistically significant difference was found between the median values of the Ateşman readability index according to Ateşman readability levels ($p<0.001$). This difference is due to the difference between the levels 40-49 and 50-59 and the levels 60-69 and 70-79. When the Ateşman reading ease scores of the web pages are evaluated according to the categories, 7.69% of the web pages are classified as easy, 80.76% as moderately difficult, and 11.53% as difficult (Table 3).

Table 3. Comparison of Ateşman readability index according to Ateşman readability levels

	Mean	Standard Deviation	Median (min.-max.)	Test Statistic	P[c]
40-49	45.9	3.98	46.8 (41 - 49)[b]	40,076	**<0.001**
50-59	55.63	2.72	56.75 (50 - 59)[b]		
60-69	62.97	2.47	62.85 (60 - 68)[a]		
70-79	72.6	2.43	72.5 (71 - 75)[a]		

a-b: There is no difference between levels with the same letter (Dunn test). [c] Kruskall Wallis H test

Table 4 shows data on Flesckincaid levels. A statistically significant difference was found between the median values of the Flesckincaid reading ease score according to the Flesckincaid text levels ($p<0.001$). This difference is due to the difference between the difficult and fairly difficult levels and the standard and fairly easy levels.

Table 4. Comparison of Flesckincaid reading ease score according to Flesckincaid text levels

	Mean	Standard Deviation	Median (min. - max.)	Test Statics	P[c]
Difficult	44.84	3.87	46.89 (38 - 48)[b]	44.025	**<0.001**
Fairly Difficult	55.61	2.5	55.84 (51 - 59)[b]		
Standard	63.18	2.57	62.96 (60 - 69)[a]		
Fairly Easy	73.57	3.33	73.55 (71 - 76)[a]		

a-b: There is no difference between levels with the same letter (Dunn test). [c] Kruskall Wallis H test

Table 5. The statistical relationship between all scores

	Ateşman Readability	Flesh-Kincaid Readability	Discern	Section 1	Section 2
Flesh-Kincaid Readability	0.998[a]; **<0.001**				
Discern	-0.160[a]; 0.259	-0.165[a]; 0.242			
Section 1	-0.186[a]; 0.186	-0.192[a]; 0.172	0.884[a]; <0.001		
Section 2	-0.124[b]; 0.380	0.141[b]; 0.319	0.946[b]; <0.001	0.730[b]; <0.001	
Section 3	-0.197[b]; 0.161	-0.209[b]; 0.136	0.944[b]; <0.001	0.796[b]; <0.001	0.938[b]; <0.001

[a] Pearson correlation coefficient, [b] Spearman's rho correlation coefficient, **r**; p

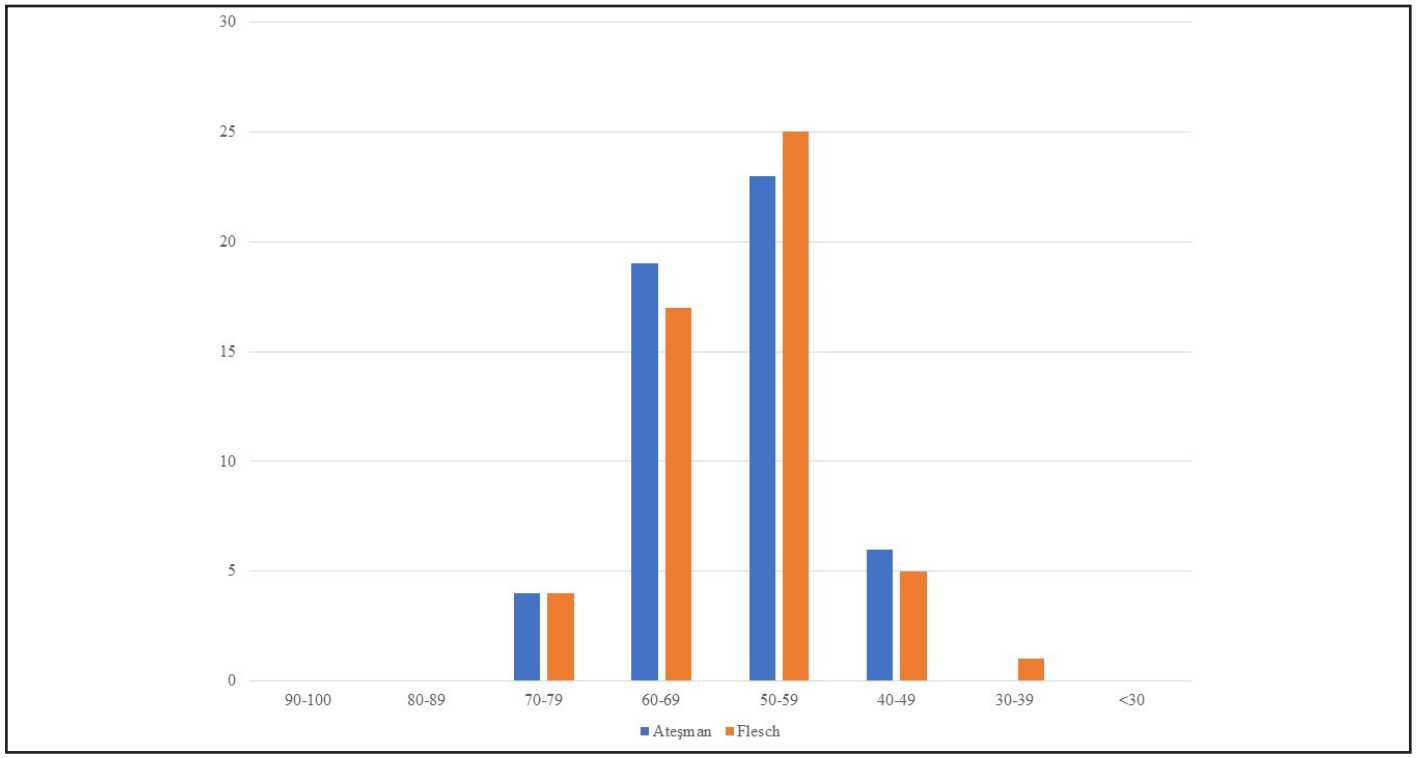

Figure 2. Categories of Ateşman Readability Index and Flesh-Kincaid Reading Ease scores

Table 5 shows the statistical evaluation of the data of all scores obtained in the study. A statistically significant positive correlation was found between Ateşman Readability Index and the Flesh-Kincaid Reading Ease score (r=0.998; p<0.001). There was no statistically significant correlation between Ateşman Readability Index and DISCERN score (p=0.259). As seen in Figure 2 which shows the number of pages on the x-axis and Ateşman/Flesh Kincaid scores on the y-axis, both readability analyses' scores are quite similar. A statistically significant positive correlation was found between DISCERN and all Section scores (p<0.001).

DISCUSSION

This study aimed to evaluate the readability of web-based information concerning post-endodontic treatment selection. In this regard, the Ateşman and Flesch-Kincaid readability evaluation terms preferred in this study are frequently used, and their consistency with the Turkish language has been demonstrated [1,9,10,12]. The scores of the current study showed that most of the websites were found to have sufficient readability. This evaluation was conducted by two different tools for correlation of the results, Ateşman and Flesh-Kincaid systems, and the independent results were similar statistically.

Besides, the quality of health information is as essential as its readability and comprehensibility [12]. Because most of the information on websites has undergone no quality control, has not been peer-reviewed, and even may not be evidence-based [6]. Therefore, the unbiased information quality of the pages was evaluated using DISCERN tool kit.

The search methodology and evaluation criteria for DISCERN were not made separately as only root canal treatment or any restoration option, and the scoring was made from the perspective of coronal restoration after root canal treatment. The first 30 web pages were selected for the evaluation because it was reported that many internet users do not look more than this number [16]. The results of this study presented that the good and excellent scores were insufficient for the included web pages. However, these results do not indicate that the selected web-based pages provide false or insufficient information on their explanation flow. It may be explained by expressing interdependent treatment options as completely independent treatment options. However, root canal treatment and coronal restoration are inseparable, and the choice of rehabilitation is a decision process that needs to be considered from multiple perspectives. For this reason, it should be emphasized that this process presents integrity while informing the patients.

Several factors affect the prognosis of the endodontically treated tooth. Besides, various factors may well affect the clinical decision-making for endodontics and also post-endodontic restoration. The development of evidence-based guidelines for endodontically treated tooth restoration is complex, with many factors that require consideration [17,18]. The paramount factor is the preservation of tooth structure of root-filled teeth [14]. Although many treatment options have been considered suitable from the past to the present, post-endodontically adhesive procedures have changed how to replace the lost structure [14,17].

Clinicians often face dilemmas regarding the most appropriate option for the restoration of a tooth after root canal treatment [17]. There is a consensus that the storation's remaining tooth structure and quality play an important role in prognosis. However, it is not certain and is still contradictory to the indications and management in the literature [14]. This is understandable when considering the development of adhesive and material technology.

Patient preferences are also one of the influencing factors regarding treatment selection [19,20]. Why, patients need to be informed accurately and adequately so that they can cooperate in their treatment options and, therefore, be able to research this information based on evidence. Evidence-based dental treatment is emphasized in healthcare, but there has been less focus on empirically demonstrating the implication of patient education and education resources [21]. Korpela et al. recommended that clinical communication skills should be part of teaching [22].
According to the DISCERN score, Alpaydın et al found the highest rates in the very poor category at 43.3% and the poor category at 44.1% [23]. Considering similar studies, this rate was reported as 47.6% fair [12], approximately 50% fair [24], and poor information quality compared to the average score [25]. The findings of our study are also compatible with previous studies and the contents were found to be fair at the highest rate according to the DISCERN score. Considering the ease of readability of previous studies, Alshehri et al [25] and Wiriyakijja et al [26] stated that the texts they examined were in the difficult category. In our study, the readability level was determined as fairly difficult. The Ateşman Readability Index and the Flesh-Kincaid Reading Ease score, which are used to evaluate the ease of readability, were both evaluated and correlated in the present study. Consistent with the findings of our study Değirmenci et al [5] determined that there was a positive correlation between both readability evaluation formulas ($r=0.801$, $p<0.001$).

The web search was limited to Turkish websites in Türkiye, so the outcomes are valid for a limited population. Selecting only two keywords can also be cited among the limitations. Keywords have been limited in this way since patients are unfamiliar with dental terminology, and their knowledge of coronal restoration is generally thought to be limited only to veneer and filling in Turkish. Another limitation of this study is that there may be

differences in the evaluation of quality and readability tools with the updates that occur in the ranking and content of the websites.

When the current results are evaluated, it is very important that the information given by health-related websites is easy to read and presents correct content [27]. In particular, it may be useful to have health-related websites evaluated by a professional before publishing a text, or to allow only professionals to share information on health-related issues, in order to prevent such problems. For patients, in addition to the knowledge gained from the clinician, it should be easy to access accurate and reliable information on websites. In particular, the fact that reliable sources are readable and understandable in public discourse ensures that those who need information stay in the appropriate ones. Accordingly, while preparing a page for website designers, it is important to provide some standards to reach the target audience correctly.

CONCLUSION

The results of this study presented that the readability distribution of the written information about post-endodontic coronal restorations on websites was acceptable to the majority. However, being readable does not indicate that it provides sufficient target technical information. It may be more informative and illustrative for patients to explain the information about post-endodontic restorations in a more relative way rather than under different headings. In this context, it can be suggested to use readability and quality scales while preparing websites for dental patient education concerning post-endodontic coronal restorations.

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Original Research

The Perceptions of Young Adults Towards Social Gender Roles

Betül Kaplan[1], Sezer Avci[1], Tülay Ortabağ[2], Doğan Erkan[3]

[1] Department of Nursing, Faculty of Health Sciences Hasan Kalyoncu University, Gaziantep, Turkey
[2] Department of Nursing, Faculty of Health Sciences, İstanbul Topkapı University, İstanbul, Turkey
[3] Mardin Education and Research Hospital,Mardin, Turkey

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Correspondence
Betül Kaplan, PhD
Address: Department of Medical Services and Techniques Hasan Kalyoncu University, Gaziantep, Turkey
E-mail: betul.tatlibadem@hku.edu.tr

ABSTRACT

Objective: This study aims to provide an in-depth knowledge of the perspectives of young adults on gender roles. There is a lack of literature in the appropriate age classes.

Methods: The study is descriptive in nature and includes 473 students. This research was conducted using a questionnaire and the Social Gender Perception Scale (SGPS) to collect data.

Results: It was determined that 52.4% of the study participants were female and 47.6% were male. 63% of the participants were affiliated with the Faculty of Health Sciences, while the remainder were students from other faculties. The average SGPS score of the participants was 95.62±18.17, but this score varied based on socio-demographic variables. Specifically, being female, possessing an undergraduate degree or higher, studying in a health sciences faculty, and having a mother who completed primary school or higher were all linked to higher SGPS mean scores. Furthermore, statistical analysis revealed a significant difference between these groups ($p<0.05$).

Conclusion: It is imperative that parents are provided with educational programs aimed at fostering knowledge of social gender roles and cultivating egalitarian attitudes and viewpoints. It is important to strategically design and execute research endeavours aimed at ascertaining the perspectives and attitudes of parents of young individuals with respect to societal gender roles.

Keywords: Social Gender, Social Gender Inequality, Social Gender Roles

INTRODUCTION

Gender refers to the inherent physiological and biological attributes that humans possess from birth, distinguishing them as either male or female [1, 2]. The concept of social gender serves to differentiate between gender, which is influenced by social and cultural factors, and biological sex. It encompasses the socially constructed roles and obligations assigned to individuals based on their gender, which are shaped by the process of socialization and the cultural attributes associated with being male or female [3]. Hence, the idea of social gender pertains not to biological distinctions, but rather to the societal perceptions, cognitions, and expectations about individuals' behaviour as either men or women [2, 4, 5]. The determination of social gender, in addition to the acquisition of gendered behaviours, is influenced by social and cultural factors, resulting in variations in its manifestations throughout different societies and throughout history [6, 7]. The process of socializing boys and girls into certain gender roles throughout their lives contributes to the understanding that social gender is a dynamic phenomenon. During the process known as "socialization" individuals continuously acquire

knowledge about societal norms and strive to conform to them throughout their lifespan [4, 7]. In essence, individuals conform to societal expectations on gender roles.

The phenomenon being referred to as "gender culture" encompasses all social evaluations pertaining to gender. Gender culture influences gender, gender roles, and social gender. It articulates, cautions, limits, and directs gender-related beliefs, attitudes, and behaviors [8]. In gender culture, "social gender roles" refers to the personality characteristics and behaviors that have historically been associated with and deemed appropriate for each gender. [9, 10]. In this context, gender roles dictate social obligations and expectations. People are born predominantly male or female, but their development within the context of gender norms is influenced by socialization [11, 12].

In contemporary culture, women show men affection and care. This is demonstrated by care and affection, submission to male authority, domestic duties, and childrearing. Conversely, men are typically associated with power and assume the responsibility of providing for the household and safeguarding the family unit [13]. In other societies, however, these examples may behave differently. In the Tibetan Mosuo community, women are the primary family leaders. The decisions regarding property, lineage, and employment are made by women. In numerous cultures, men are more passive than women, including the Minangkabau community of Indonesia, the Akan people of Ghana, the Bribri people of Costa Rica, and the Nagovisi community of South Bougainvillea, western New Guinea [7].

The varying societal expectations placed upon individuals based on their gender, as well as the corresponding beliefs held by society, contribute to the development of gender-specific behaviors in individuals. The existing body of research indicates that there are notable disparities in the societal expectations and perceptions around gender roles, particularly in relation to employment, social interactions, marriage, and family dynamics [1, 5, 9]. Prior to accepting the parental position within the context of family life, individuals may demonstrate egalitarian behaviors with regard to gender roles. However, after assuming the role of parent, individuals may display more conservative behaviours [14]. The examination of the societal roles ascribed to individuals based on their gender within a predominantly traditional social structure is a crucial endeavour [5]. It is imperative to comprehend the implications of these roles on the younger generation, their individual interactions with society, and their lived experiences throughout this developmental process, while refraining from disregarding their significance [15]. According to scholarly literature, empirical findings indicate that young males tend to demonstrate a more conventional mindset [2, 13]. Research has indicated that there is a higher propensity among young individuals, both males and females, to emulate their parents as role models during the process of shaping their social gender roles [9]. According to Boehnke a separate study indicated that the offspring of parents with higher levels of education and employed mothers had a greater inclination towards egalitarian gender norms [16]. Consequently, it is crucial to emphasize the significance of parental influence [15] and family structure in the formation of social gender perception [9, 13]. According to a study conducted by Marks et al., there exists a notable disparity in gender role attitudes between parents and children among family units adhering to conventional family structures or traditional parenting styles [17]. The younger generation, who will assume the role of future parents, has significant obligations in fostering an egalitarian understanding of societal gender roles among their offspring. The allocation of tasks and obligations to girls and boys within the family unit is influenced by factors such as schooling and the social environment. Consequently, children acquire their social gender identity through these mechanisms [18].

Main Points;

- This study aims to enhance the understanding of gender roles among young individuals.
- It is important to strategically design and execute research endeavors aimed at ascertaining the perspectives and attitudes of families of young individuals pertaining to gender roles.

According to the Convention on the Elimination of All Forms of Discrimination Against Women (CEDAW), our country exhibits both legal regulations that adhere closely to international standards and instances of discrimination, infringement, and violent practices that are deemed entirely unacceptable in contemporary societies. According to Savaş, Turkey's position in the "Social Gender Inequality Index" was 64th out of 188 nations, while in the "Global Gender Gap Index" it placed 131st out of 144 countries [7]. However, it is worth noting that Turkey

did not attain the expected level of achievement in these rankings. It is imperative that all stakeholders exert concerted efforts to enhance the social and economic status of women within our nation, with a particular focus on addressing and ameliorating adverse indicators. In comparison to other member nations of the Organisation for Economic Co-operation and Development (OECD), Turkey is required to exert more endeavors in order to enhance women's employment rates and establish a state of gender equality [19]. When examining OECD nations, it is seen that the disparity in wages between males and females is most pronounced in Korea, with a margin of 34.6%. Conversely, Romania has the lowest wage gap at 1.5%. According to the OECD (2017), the rate in Turkey is at 6.9% [20].

Based on the aforementioned data, an examination of scientific literature pertaining to social gender, gender culture, and gender equality reveals that the establishment of parity between men and women is widely regarded as the primary catalyst for constructing a society that is sustainable, equitable, and contemporary in nature. Given the scarcity of existing research pertaining to the specific age cohorts under consideration, the primary objective of this study was to enhance understanding and knowledge regarding the experiences and characteristics of young individuals. Furthermore, acquiring data from this study will provide a valuable contribution to the existing body of literature.

MATERIALS AND METHODS

Sample

The investigation was conducted at the Hasan Kalyoncu University. In addition, data was collected from student dorms on the university campus, all of whom were at least 18 years of age and did not have any known communication impairments. Students from the faculties of health sciences, architecture, engineering, law, science and literature, space and aviation, visual arts, economics, and administrative sciences were included in the study. The sample size was determined using the "G. Power-3.1.9.2" program, which yielded an 80% power level. The purpose of this study was to determine the impact of baseline student characteristics, such as age, gender, and educational level, on SGPS mean scores. Moreover, the student t-test was employed for statistical analysis. When the effect size is 0.34, the alpha level is 0.05%, and the theoretical power is 80%, 235 students were determined to be the sample size for the study. The research sample consisted of 473 students, which represents 72.35 percent of the total population.

Procedure

The data for this study were collected using a questionnaire comprised of the Introductory Features Form and the Gender Perception Scale, which was devised based on a comprehensive evaluation of the pertinent literature. The sociodemographic factors were restricted in scope and centered on the scale responses from students. The survey questionnaire includes inquiries regarding gender, marital status, educational attainment of the respondent's mother, personal educational attainment, and department affiliation. The study incorporated two research inquiries.

Question 1: Does a correlation exist between the socio-demographic features of students and their SGPS scores?

Question 2: Does a correlation exist between students' perspectives on social gender and the Social Gender Perception Scale (SGPS)?

Prior to commencing the study, requisite authorizations were acquired from the Ethics Committee for Non-Interventional Research at Hasan Kalyoncu University Faculty of Health Sciences (Date: 16.12.2020, Decision No: 2020/111), as well as from the Chief Physician of the Research and Application Hospital where the study was conducted. All study participants were provided with information on the research, and their consent was gained by written or verbal means. Additionally, participants were advised of their right to withdraw from the study at any point. The research conducted in this study followed the ethical principles outlined in the Declaration of Helsinki.

Measures

Introductory Features Form

The researchers have prepared an Introductory Features Form that includes elements pertaining to the sociodemographic features of the participants, such as age and gender, as well as their perspectives on social gender.

Social Gender Perception Scale (SGPS)

The Cronbach alpha reliability coefficient of the SGPS, as developed by Altınova and Duyan, is reported to be 0.87 [4]. The scale, comprising a comprehensive set of 25 elements, does not incorporate any subscales. The questions on the scale were assessed using a 5-point Likert Scale, which included the response options of "Strongly Agree," "Agree," "Neither Agree Nor Disagree," "Disagree," and "Strongly Disagree." The upper

limit of the scoring scale for pupils is 125, while the lower limit is 25. Elevated scores derived from the scale signify that the student possesses an egalitarian stance on social gender roles, whilst diminished scores suggest a propensity for traditional attitudes towards social gender roles. The items on the Perception Scale that were oriented in a negative direction were subjected to reverse scoring throughout the evaluation process. The aforementioned items include numbers 2, 4, 6, 9, 10, 12, 15, 16, 17, 18, 19, 20, 21, 24, and 25.

Statistical Analysis

The data gathered in the study was subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS) for Windows 22.0 software in a computerized setting. The conformity of the measurement values acquired in the context of the study was assessed using the "Shapiro-Wilk Test". Descriptive statistics for continuous numeric variables were represented using the mean ± standard deviation and the median (interquartile range (IQR) within a 95% confidence interval. Categorical variables were represented using numbers (n) and percentages (%). The independent samples t-test was employed to assess the differences between two distinct groups and compare the scale's average scores. In the context of statistical decision-making, a p-value equal to or less than 0.05 was deemed to possess statistical significance.

RESULTS

In the study, it was found that 52.4% of the participants were identified as female, while 47.6% were identified as male. The average age for female students was determined to be 21.42±2.47, but for male students, it was 22.28±1.82. A majority of the participants (63%) in our research study are enrolled in the Faculty of Health Sciences, while the remaining minority (37%) are pursuing their studies in faculties outside of the aforementioned field. Mothers of participants had elementary or lower education in 74.4% of cases, and secondary or higher education in 29.6% of cases (Table 1).

Table 1. Distribution of Sociodemographic Characteristics of Young People (N=473)

Characteristics	Number	Percentage
Gender		
Female	248	52.4
Male	225	47.6
Marital status		
Married	10	2.1
Single	463	97.9
Educational status		
Associate degree	28	5.9
Graduate degree and higher	445	94.1
Department		
Health-related faculties	298	63.0
Other faculties	175	37.0
Mother's educational status		
Elementary school and lower	333	70.4
Higher than elementary school	140	29.6
Total	473	100.0

The average SGPS of the students involved in the study was determined to be 95.62±18.17. The scale's minimum and highest results are 39 and 125, respectively (Table 2).

Table 3 presents a comparison of the sociodemographic features of the students and the mean scores on the SGPS. The analysis revealed a statistically significant association between educational status, gender, department of study, maternal education level, and scale scores (p=0.001 for all variables). Based on the findings, it was concluded that female students studying at the health sciences faculty, who possess a bachelor's degree or above, and whose maternal education level exceeds elementary education, had higher mean scores in the SGPS..

Table 4 displays a comparison of the participants' perspectives on social gender and their corresponding SGPS mean scores. The results of the study indicated that students who had a favorable view towards each item exhibited significantly higher mean scores on the scale (p<0.05 for all).

Table 2. Social Gender Perception Scale Mean Scores (N=473)

	Groups	X̄±Ss	Min-Max Score Obtained from the scale	Min-Max Score That can be obtained from the scale
Gender	Female student	105.55±13.09	39-125	25-125
	Male student	84.68±16.66	39-125	

Table 3. Comparison of Social Gender Perception Scale Mean Scores by Sociodemographic Characteristics of Young People (N=473)

Sociodemographic Characteristics and Groups	Social Gender Perception Scale Mean Scores and Test			
	n (%)	X̄± Ss	t	p
Gender				
Female	248 (52.4)	105.55±13.09	15.041	0.001*
Male	225 (47.6)	84.68±16.66		
Educational status				
Associate degree	28 (5.9)	81.89±16.53	4.191	0.001*
Graduate degree and higher	445 (94.1)	96.48±17.94		
Department				
Health-related faculties	298 (63.0)	101.76±15.83	10.676	0.001*
Other faculties	175 (37.0)	85.16±17.14		
Mother's educational status				
Primary school and lower	333 (70.4)	92.91±18.19	5.138	0.001*
Higher than primary school	140 (29.6)	102.07±16.49		

***** *p<.01*

Upon examining the gender-based comparison of students' perspectives on gender, it was observed that male students tended to hold a more conventional viewpoint, as seen in Table 5.

DISCUSSION

The present study aimed to examine the perceptions of university students about the influence of social gender and explore potential variations in this connection based on certain demographic factors.

In the present study, the Social Gender Perception Scale was utilized to assess the aggregate score achieved by individuals in the young age group. The acquired scores were found to vary between 39 and 125, with a mean score of 95.62 and a standard deviation of 18.17. There exist several research that have yielded comparable findings to those presented in our study [9, 21]. This study aimed to examine the relationship between sociodemographic factors and social gender perception levels among young individuals. Consistent with previous research findings [2, 5], it was observed that female students enrolled in health sciences programs, with a bachelor's degree or higher, and whose mothers had attained an education level beyond primary education, exhibited higher mean scores on the social gender perception scale [22].

Table 4. Comparison of Young People's Views on Social Gender with the Scale Mean Score (N=473)

Participants' Views	Social Gender Perception Scale Mean Scores and Test			
	n (%)	X̄± Ss	t	p
The most important role of the woman is to cook for her family.				
Yes	88 (18.6)	81.68±17.00	8.561	0.001*
No	385 (81.4)	98.81±16.90		
A man should have the last word on decisions at home.				
Yes	89 (18.8)	81.24±16.26	8.953	0.001*
No	384 (81.2)	98.95±16.94		
Marriage prevents a woman from working.				
Yes	47 (9.9)	78.96±20.33	6.945	0.001*
No	426 (90.1)	97.46±16.97		
A woman having a baby boy increases her value.				
Yes	27 (5.7)	90.56±16.85	1.493	0.136
No	446 (94.3)	95.93±18.22		

Working women can spare enough time for their children.				
Yes	262 (55.4)	103.17±15.39	11.351	0.001*
No	211 (44.6)	86.24±16.99		
The most important task of a man is to support his home.				
Yes	187 (39.5)	88.07±16.99	7.741	0.001*
No	286 (60.5)	100.55±17.23		
Women can succeed in management and politics.				
Yes	430 (90.9)	97.99±16.45	9.841	0.001*
No	43 (9.1)	71.91±17.76		
If women are pregnant, men should be preferred in job applications.				
Yes	53 (11.2)	74.74±15.39	9.714	0.001*
No	420 (88.8)	98.25±16.75		
The woman must tolerate violence to protect her family.				
Yes	23 (4.9)	84.57±15.13	3.016	0.003*
No	450 (95.1)	96.18±18.15		
Men should also do household chores such as laundry, dishes, cleaning.				
Yes	440 (93.0)	97.15±17.29	7.021	0.001*
No	33 (7.0)	75.21±17.59		
Only a man should provide for a family.				
Yes	32 (6.8)	67.00±13.61	10.177	0.001*
No	441 (93.2)	97.70±16.65		
Girls should be given as much freedom as boys.				
Yes	379 (80.1)	100.11±16.00	12.419	0.001*
No	94 (19.9)	77.51±14.92		
If a woman can’t have children, a man should remarry.				
Yes	28 (5.9)	81.96±13.13	4.169	0.001*
No	445 (94.1)	96.48±18.11		
Everything the man says at home must be done.				
Yes	20 (4.2)	74.50±18.65	5.470	0.001*
No	453 (95.8)	96.55±17.60		
A woman should be able to oppose her husband if necessary.				
Yes	413 (87.3)	98.26±16.71	8.964	0.001*
No	60 (12.7)	77.43±17.54		
The saying: “A woman without a husband is like a house without an owner.” is true.				
Yes	87 (18.4)	78.30±15.70	11.023	0.001*
No	386 (81.6)	99.52±16.33		

**p<.01*

Table 5. Comparison of Gender Perspectives among Young Individuals (N=473)

Participants' Views	Social Gender Perception Scale Mean Scores and Test			
	Female Student	Male Student		
	n (%)	n (%)	t	p
A man should have the last word on decisions at home.				
Yes	16 (6.5)	73 (32.4)	52.177	0.001*
No	232 (93.5)	152 (67.6)		
Marriage prevents a woman from working.				
Yes	12 (4.8)	35 (15.6)	15.140	0.001*
No	236 (95.2)	190 (84.4)		
Women can succeed in management and politics.				
Yes	243 (98.0)	187 (83.1)	31.575	0.001*
No	5 (2.0)	38 (16.9)		
If women are pregnant, men should be preferred in business applications.				
Yes	8 (3.2)	45 (20.0)	33.362	0.001*
No	240 (96.8)	180 (80.0)		

In terms of participant gender, it was shown that female students (M=95.84±11.54) exhibited significantly higher scores in social gender perception compared to male students (M=72.09±14.18). (p=0,001). Numerous research undertaken within our nation have consistently revealed that female students exhibit greater levels of gender role attitudes or perceptions compared to their male counterparts [23-27]. The study conducted by Özpulat examined a sample of 247 university students and found that female students exhibited higher gender perception ratings in comparison to their male counterparts [21]. Seçkin and Tural conducted a study to investigate the attitudes of classroom teacher candidates towards social gender roles [28]. The findings revealed that female teacher candidates exhibited significantly more egalitarian attitudes towards social gender roles compared to their male counterparts. A research conducted by Kodan Çetinkaya at Ataturk University including 207 students yielded comparable findings, indicating that female students had a greater inclination towards egalitarianism [11]. The observed tendency of girls to exhibit a more egalitarian mindset [29] can be attributed to their heightened exposure to the adverse effects of gender inequality within societal and familial contexts, hence motivating their desire for equitable standing alongside males. The aforementioned discovery provides a partial explanation for the persistence of conventional beliefs among males, as well as their reluctance to embrace gender equality and concerns about potential losses in an egalitarian society [30].

Our research findings indicate that students enrolled in health-related faculties exhibit a higher degree of egalitarianism in their attitudes regarding social gender roles compared to students from other faculties. Previous research has found that students enrolled in the health department have a more egalitarian perspective towards gender roles [2, 31-33]. This outcome might be attributed to the fact that individuals enrolled in health-related faculties are likely to assume roles in delivering healthcare services to the community in the forthcoming years.

Furthermore, our study involved a comparison between the perspectives of young individuals on social gender perception and the mean scores obtained from a standardized scale. The study revealed that the average scores of the younger individuals who expressed a favorable viewpoint for each item were significantly elevated. Hence, although this outcome is deemed favorable for our research, the findings that elucidate participants' perspectives on social gender beyond the established parameters have augmented the importance of our study. The findings presented in this study are limited in scope and pertain exclusively to the context of this research. It is argued that women ought to strive for social and economic autonomy beyond the confines of their domestic responsibilities. In our study, an examination was conducted to assess the social gender perspective of young individuals, with a specific focus on comparing these perceptions based on gender. The findings

revealed that males tended to have more traditional viewpoints in relation to propositions about social life. According to our research findings, male students exhibited a conventional perspective while considering the statements "The primary responsibility of women is to prepare meals for their families" and "Men should possess ultimate decision-making authority within the household." A research was done to ascertain the perspectives of male students regarding gender roles. According to a study conducted by Adana et al. there is evidence to suggest that males who hold traditional views of gender roles, namely believing that women should primarily engage in domestic duties, bear children, and provide care for senior family members, tend to disapprove of their wives pursuing employment opportunities [34]. Furthermore, these individuals exhibit a lack of belief in gender equality. The findings of this study indicate that societal perceptions regarding male dominance remain pervasive, as males continue to occupy more conventional roles. It is evident that the inclusion of qualitative group research is important in order to yield more favorable outcomes pertaining to this particular topic. When examining the influence of parents on their children's attitudes, it becomes evident that a significant level of maternal education can result in increased engagement in professional pursuits and improved exemplification of gender roles, as supported by Antill et al. and Davis & Greenstein [30, 35]. Moreover, it is crucial to incorporate themes that underscore the significance of women's education via media coverage. Furthermore, it is imperative to highlight the need of modifying some professional designations that explicitly state gender, such as replacing "businessman" with "businessperson" and "man of science" with "scientist." This emphasis should be communicated through the media as a means to address and mitigate gender imbalance.

Limitations

Due to the presence of diverse cultural structures across its areas, Turkey may only be accurately generalized within regions that share comparable cultural characteristics.

CONCLUSIONS

Consequently, it is important to design and execute research endeavors aimed at elucidating the perspectives and attitudes held by the families of young individuals with relation to gender roles. It is important to ensure that parents are provided with educational programs aimed at raising understanding about societal gender roles and fostering egalitarian attitudes and viewpoints. The panels pertaining to social gender should be encouraged to acknowledge the influence of societal norms on their conventional viewpoints, and to adopt an egalitarian standpoint. It is imperative to address the societal gender prejudices that hinder girls' access to education and are deeply ingrained in our collective consciousness. Furthermore, it is imperative that the curriculum throughout all levels of the education system, ranging from basic schools to university education, incorporates course materials pertaining to societal gender equality. In order to modify the prevailing conventional mindset among male students, particularly those residing in student dorms within institutions, it is proposed that they be allocated responsibilities pertaining to educational endeavors, such as participation in conferences and panels. Peer education initiatives can be organized to involve male pupils in the process. It is important to promote the formation of organizations or student communities that focus on social gender equality and actively involve male students in these initiatives.

Informed Consent: Informed consent document was obtained from the study participants.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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Ethical Approval: Hasan Kalyoncu University Faculty of Health Sciences Ethics Committee for Non-Interventional Research (Date: 16.12.2020, Decision No: 2020/111).

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This study has established that males exhibit a greater propensity for adhering to conventional ideas. Encouraging the involvement of male students in activities that promote gender equality is crucial for altering their adherence to conventional ideas.

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Original Research

Dietary Zinc Status in Offspring of Pregnant Rats Fed on a Zinc-Deficient Diet Is Associated with Serum Albumin, Ast, and Alt Levels

Meltem Gumus[1], Saltuk Bugra Baltaci[2]

[1] Department of Child Health and Diseases, Selcuk University, Medical Faculty, Konya-Turkey
[2] Department of Physiology, Regenerative and Restorative Medical Research Center, Istanbul Medipol University, Istanbul, Turkey

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Correspondence
Meltem Gumus, MD
Address: Department of Child Health and Diseases, Faculty of Medicine, Selcuk University, Konya, Turkey
e-mail: meltem.dorum@selcuk.edu.tr

ABSTRACT

Objective: This study was carried out to investigate whether dietary zinc status is associated with serum albumin, AST and ALT levels in male offspring of mother rats fed a zinc deficient diet.

Methods: The study was carried out on male offspring (Groups 1, 2, 3) born to rats fed a zinc deficient diet and on male offspring (Group 4) born to mothers fed a standard diet. Group 1: Zinc deficient, Group 2; standard rat chow, Group 3: Zinc supplemented diet. Animals of group 4 were used as control group. After the completion of the experimental stages of the study, albumin, AST, ALT, free and total bilirubin levels in serum samples taken from animals were determined by spectrophotometric method.

Results: Dietary zinc deficiency (group 1) significantly decreased serum albumin values ($p<0.004$). Animals in both the zinc deficient (Group 1) group and the Group 2 animals born to mothers fed a zinc deficient diet and fed standard rat chow had the highest AST and ALT levels ($p<0.001$).

Conclusion: The present study is the first to show that dietary zinc status can directly affect liver function in rats born to zinc deficient mothers by causing changes in serum albumin, AST and ALT levels.

Keywords: Maternal zinc deficiency, zinc, Albumin, AST, ALT, male offspring rat

INTRODUCTION

The liver, which is the main organ of zinc metabolism, is also critical in regulating and maintaining the zinc balance of the body [1]. Zinc plays a role in many enzymatic reactions of the liver, especially in the urea cycle [2]. Low zinc levels in liver patients were first reported by Vikbladh [3] in 1951. In later studies, it has been shown that both liver and serum zinc decrease in chronic liver diseases [4, 5].

Patients with liver cirrhosis have widespread zinc deficiency [6]. The levels of this deficiency are closely related to the severity of the disease [7]. Zinc deficiency in liver patients is also affected by changes in carbohydrate and protein metabolism. Another factor that can lead to zinc deficiency in liver diseases is changes in albumin concentration. Albumin is the main circulating transporter of zinc [8].

Decreased albumin levels in liver diseases also lead to a decrease in zinc absorption, leading to the progression of liver disease [9]. Zinc deficiency is seen in 85.6% of liver patients [10]. Zinc deficiency in these patients may also be caused by metabolic disorders such as hepatic steatosis, iron overload, insulin resistance [11]. Zinc supplementation for liver patients improves these disorders [10, 11].

Aminotransferases; Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most sensitive tests showing liver tissue damage [12]. They are released from the

damaged liver cell. In cholestatic diseases, mild elevations can be seen due to hepatocyte damage caused by bile stasis. Since ALT is found in low concentrations in other tissues such as muscle, it is more specific to liver diseases [12, 13].

The aim of this study is to investigate how zinc deficiency and its administration affect circulating albumin, AST , ALT, direct and total bilirubin levels in male offspring rats born to mothers fed a zinc-deficient diet during pregnancy.

MATERIALS AND METHODS

The study was carried out at Selcuk University Experimental Medicine Research and Application Center. The study protocol was approved by the animal ethics committee of the same center (decision dated 27.03.2020 and numbered 2020-15).

Animal Material and Groups

The juveniles used in the study were obtained from 20 adult female rats, 15 of which were fed a zinc-deficient diet during their pregnancies and 5 of which were fed with standard rat chow during their pregnancies.

Feeding of Animals

The rats were fed ad libitum and kept in 12-h light/dark cycle. Animal feed were obtained from Selcuk University Experimental Medicine Research and Application Center as normal standard rat feed (in pellets) (Table 1).

Energy content was 367 (11%) kcal / kg for Fat, 768 (24%) kcal / kg for Protein and 2,091 (65%) kcal / kg for Carbohydrates.

Vitamin mix: The vitamin mix of feed given to experimental animals contains vitamins A, D3, E, K, B1, B2, B6, B12 and nicotinamide, folic acid, D-biotin and choline chloride.

Main Points;

- This study shows that dietary zinc status causes changes in serum albumin, AST and ALT levels in male offspring born to mothers fed a zinc deficient diet during pregnancy.
- This study is the first to show that dietary zinc status can directly affect liver function in rats born to zinc-deficient mothers.

Table 1. Content of some trace elements and minerals in standard rat feed

Content	Value	Unit
Aluminium	79.37	mg/kg
Iron	3,484.07	mg/kg
Iodine	1.66	mg/kg
Cobalt	0.34	mg/kg
Copper	12.81	mg/kg
Manganese	95.06	mg/kg
Molybdenum	1.10	mg/kg
Sulfur	1,141.22	mg/kg
Selenium	0.25	mg/kg
Zinc	95.18	mg/kg
Calcium	7,012	mg/kg
Potassium	8,797	mg/kg
Magnesium	2,220	mg/kg
Sodium	2,128	mg/kg
Phosphorus	5,014	mg/kg

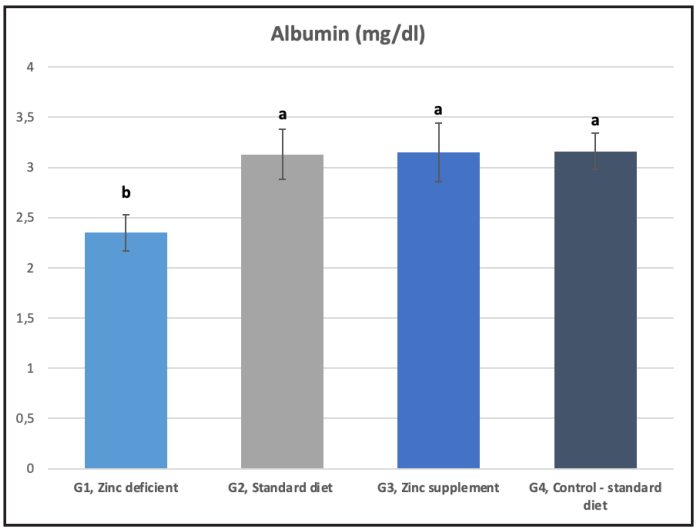

Figure 1. Serum Albumin Levels of Study Groups

Means with different superscripted letters in the same column are statistically significant a>b (P<0.05).

Pairwise Comparison P Values of the Groups According to the Mann-Whitney U Test Results:
Albumin:G1-G2:0,004; G1-G3:0,000; G1-G4:0,000; G2-G3:0,989; G2-G4:0,939; G3-G4:0,915

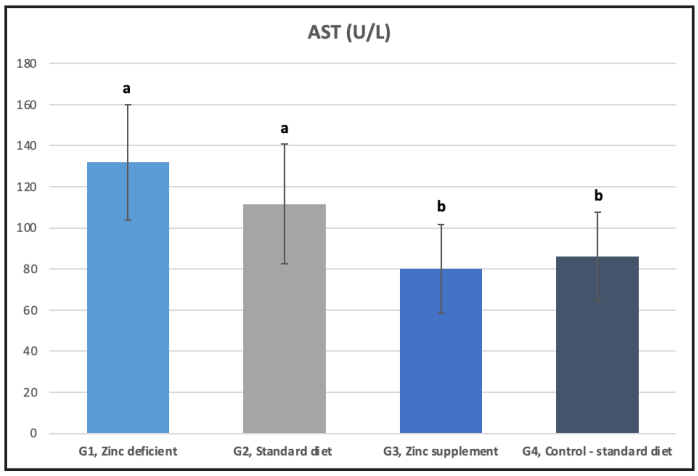

Figure 2. Serum AST Levels of Study Groups

*Means with different superscripted letters in the same column are statistically significant a>b (P<0.05).

Pairwise Comparison P Values of the Groups According to the Mann-Whitney U Test Results:
AST=G1-G2:0,294; G1-G3:0,000; G1-G4:0,001; G2-G3:0,041; G2-G4:0,030; G3-G4:0,951

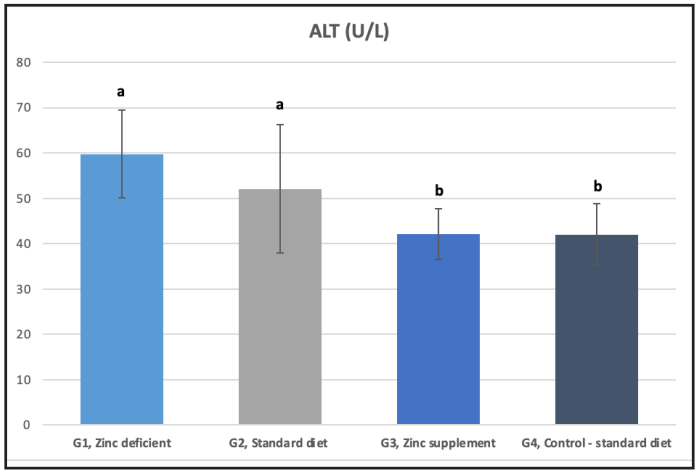

Figure 3. Serum ALT Levels of Study Groups

*Means with different superscripted letters in the same column are statistically significant a>b (P<0.05).

Pairwise Comparison P Values of the Groups According to the Mann-Whitney U Test Results:
ALT.G1-G2:0,297; G1-G3:0,001; G1-G4:0,001; G2-G3:0,113; G2-G4:0,040; G3-G4:1,000

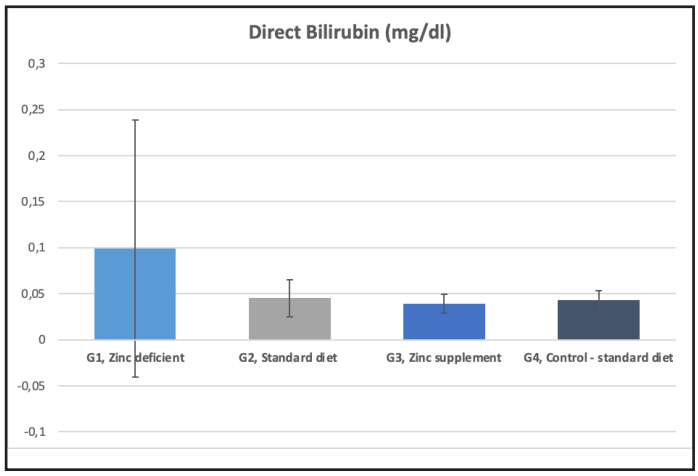

Figure 4. Direct Biluribin Levels of Study Groups

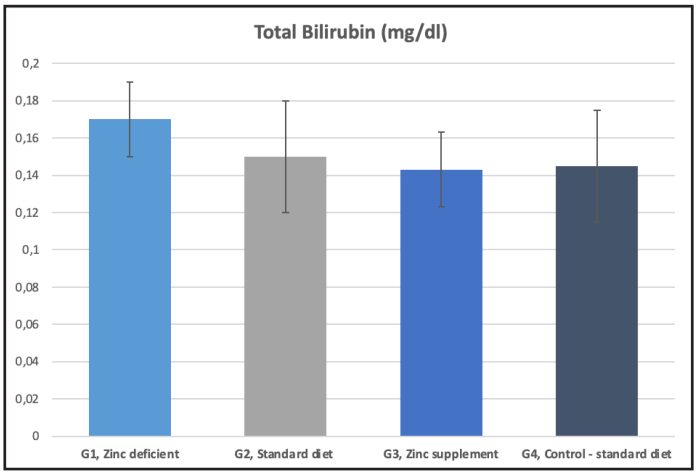

Figure 5. Direct Biluribin Levels of Study Groups

Experimental Groups

Offspring rats (Groups 1, 2, 3) born to mothers fed a zinc deficient diet (2.8 mg/kg zinc) and offspring rats born to mothers fed standard rat chow (Group 4) were separated from their mothers at 21 days of age. Male offspring rats were divided into groups as follows:

Group 1, Zinc deficient: Offspring rats in this group were fed a zinc deficient diet (2.8 mg/kg zinc) for 70 days [14].

Group 2, Standard Diet: Animals in this group were fed standard rat chow for 70 days.

Group 3, Zinc supplemented: Animals in this group received zinc supplementation (5 mg/kg/day ip zinc sulfate) until the end of the study (70 days) in addition to standard rat chow.

Group 4, Control: Control animals in this group were fed with standard rat chow.

Informed Consent

After the completion of the experimental stages of the study, all animals were sacrificed under general anesthesia and serum samples were taken. General anesthesia was administered to all animals (with intramuscular administration of a combination of Ketalar (60 mg/kg), Parke-Davis and xylazine (5 mg/kg) "Rompun, Bayer") to avoid animal suffering.

Biochemical Analyzes

Biochemical analysis were carried out on 3 ml serum samples obtained from blood from animals. Albumin (mg/dl), AST (U/L), ALT (U/L), free and total bilirubin levels (mg/dl) in the obtained serum samples were determined by spectrophotometric method in the Abbott Architect c8000 device (Abbott Architect c8000 Chemistry Analyzer).

Statistical Analysis

The mean and standard errors of the data in the study were calculated. Kruskal-Wallis H test was used for the difference between the groups. Mann-Whitney U test was used to determine which group the difference consisted of. A $p<0.05$ level was considered significant.

RESULTS

The lowest serum albumin values in our study were obtained in group 1 fed a zinc deficient diet ($p<0.004$). Serum albumin values of groups 2, 3 and 4 were not different from each other (Graphic 1). In our study, the highest AST and ALT levels were obtained in Group 1, which was fed with a zinc-deficient diet after maternal zinc deficiency was created, and in Group 2, which was fed with a normal diet after maternal zinc deficiency was created ($p<0,001$). After the maternal zinc deficiency was established, the AST and ALT levels of Group 3, which was supplemented with zinc in addition to the standard rat diet, were higher than Groups 1 and 2 ($p<0,001$), and were not different from the control group (Group 4) (Graphics 2, 3). Direct and total bilirubin values did not differ between the groups (Graphics 4, 5).

DISCUSSION

An important trace element, zinc is associated with many events from growth, reproduction, immune functions to aging [15]. The liver can increase the bioavailability of many elements, especially zinc [16]. In this respect, a relationship between liver and zinc is inevitable. At the same time, the deficiency of zinc, which is a powerful antioxidant element, in the body may contribute to deterioration in liver functions and/or the progression of chronic liver diseases [16, 17]. Yang et al. [17] reported a significant decrease in serum albumin levels of the patient group whose zinc was found to be significantly lower than the controls in a study performed on patients with cirrhosis. Similarly, it has been reported that serum zinc and albumin levels are significantly lower in patients with infections caused by acute phase response activation [18]. Morisaku et al. [19] found low serum zinc and albumin levels in patients with malignant lymphoma. The same researchers reported that their findings were the first to show that albumin was correlated with zinc in malignant lymphoma [19]. In our study, the lowest serum albumin values were obtained in group 1 fed a zinc-deficient diet. This finding shows that dietary zinc deficiency suppresses albumin concentration in rats with maternal zinc deficiency. Reporting that albumin levels decrease in parallel with low zinc levels in various diseases, especially liver diseases[17-19] is in strong agreement with the low zinc and albumin levels we obtained in our study.

Elevated AST levels have been demonstrated in patients with hepatitis B liver cirrhosis, with decreased serum zinc levels. In the same study, it was reported that as the disease progresses, the decrease in zinc levels and the increase in AST levels occur more severely [20]. Reporting that increased AST and ALT levels in protein-deficient rats are prevented by zinc supplementation is a critical finding for the relationship between zinc and AST and ALT [21]. Similarly, Yousef et al. [22] reported that zinc deficiency causes an increase in AST and ALT levels in growing rats. In conclusion, zinc has a critical relationship with AST and ALT levels, which are used as markers for liver dysfunction.

In the current study, the highest AST and ALT levels were obtained in Group 1 fed with zinc deficient diet after maternal zinc deficiency was established and Group 2 fed with normal diet after maternal zinc deficiency was established. High AST and ALT levels, especially in Group 2, are a very important finding. Because the animals in this group with maternal zinc deficiency were fed with a normal diet, but there was no suppression in AST and ALT levels.However, in our study, AST and ALT levels of Group 3, which was supplemented with zinc in addition to the standard rat feed after maternal zinc deficiency was created, were lower than Group 1 and 2, and were not different from the control group (Group 4).

In our study, direct and total bilirubin values did not differ

between the groups. We could not find a study that directly deals with the relationship between bilirubin and zinc in medline scans.

A report was published in 2013, stating that severe cholestasis seen in 3 premature babies in a healthcare facility in the United States can be prevented with zinc supplementation (Centers for Disease Control and Prevention "CDC" 2013) [23]. However, there is no detailed breakdown of the said report. We did not find an association between maternal zinc deficiency or zinc status and bilirubin levels in the current study.

In the current study; Albumin levels, which were significantly suppressed in zinc deficiency, reached control values with standard feed or zinc application. However, serum AST and ALT levels were significantly higher both in the group fed with a zinc deficient diet after maternal zinc deficiency was established (group 1) and in the group fed with a normal diet after maternal zinc deficiency was established (group 2). In our study, it is an important finding that feeding the pups born to mothers fed a zinc-deficient diet during pregnancy with standard rat chow for 70 days did not abolish the increase in AST and ALT levels. This critical finding shows that liver development and therefore liver functions of offspring born to mothers with zinc deficiency during pregnancy may be adversely affected.

CONCLUSION

The present study is the first to show that dietary zinc status can directly affect liver functions by causing changes in serum albumin, AST and ALT levels in rats with maternal zinc deficiency.

In possible future studies, revealing the effects of different doses of zinc in the diet may provide us with more concrete information.

Author Contributions: MG and SBB made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; MG and SBB drafted the work or revised it critically for important intellectual content, approved the version to be published. The authors declare that all data were generated in-house and that no paper mill was used.

Conflict of interest: The authors declare that they have no potential conficts of interest to disclose.

Research Data Policy and Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Ethical Approval: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Experimental Animals Ethics Board of Selcuk University Experimental Medicine Research and Application Center (2020-15). This research was performed on the animals (rat).

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Original Research

Assessing the Pros and Cons of Performing Orthognathic Surgery in Patients Undergoing Orthodontic Aligner Treatment

Ricardo Grillo[1,2], Alexandre Meireles Borba[3,4], Mariana Aparecida Brozoski[1], Antônio Augusto Campanha[5], Yunus Balel[6], Andréia Aparecida Traina[1], Maria da Graça Naclério-Homem[1]

[1] Department of Oral and Maxillofacial Surgery, Traumatology and Prosthesis – Faculty of Dentistry of the University of São Paulo, São Paulo-SP, Brazil
[2] Department of Oral and Maxillofacial Surgery, Faculdade Patos de Minas, Brasília-DF, Brazil
[3] Research Program on Integrated Dental Sciences, Faculty of Dentistry of the University of Cuiaba – UNIC, Cuiabá-MT, Brazil
[4] Department of Oral and Maxillofacial Surgery, General Hospital of Cuiaba, Cuiabá-MT, Brazil
[5] Department of Oral and Maxillofacial Surgery, Universidade Paulista, Campinas-SP, Brazil
[6] T.R. Ministry of Health, Sivas Oral and Dental Health Hospital, Sivas, Turkey

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Correspondence
Yunus Balel, DDS, MS
Address: T.R. Ministry of Health, Sivas Oral and Dental Health Hospital, Sivas, Turkey
E-mail: yunusbalel@hotmail.com

ABSTRACT

Objective: Orthodontic aligners have become one of the most requested treatments by patients. This study evaluated maxillofacial surgeons´ experience of using orthodontic aligners in preparation for orthognathic surgery.

Methods: A survey using an online platform was used to identify some key points about maxillofacial surgeons´ prior experiences with orthodontic aligners in the context of orthognathic surgery. Participants were asked to discuss their experience with orthognathic surgery preparation through orthodontic aligners.

Results: In total, 396 surveys were sent, the sample consisted of 92 respondents. The experience of maxillofacial surgeons on this topic is not very large, some of them (45.65%) have not had contact with orthodontic aligners. Advantages include patient convenience and easy postoperative hygiene, while some disadvantages include inefficient postoperative occlusal stability and intermaxillary block and some difficulties in using elastic bands. A very helpful explanation to solve some problems was highlighted by the surgeons, including a more detailed conference on orthodontic preparation. Maxillary segmentation must be avoided according to the majority of surgeons.

Conclusion: The results of the study indicate that not all cases are suitable for orthognathic surgery prepared with orthodontic aligners. While orthodontic aligners offer advantages such as patient-friendliness and improved hygiene, the lower number of surgeons reporting these benefits compared to the disadvantages underscores challenges related to postoperative occlusal stability and limitations with intermaxillary blocks and elastic band usage.

Keywords: Orthognathic Surgery; Orthodontic Appliances; Surveys and Questionnaires; Humans; Orthognathic Surgical Procedures

INTRODUCTION

The field of orthognathic surgery planning has witnessed significant advancements over the past two decades [1]. The transition from traditional plaster surgery to digital planning

has brought about a remarkable evolution [2–4]. The precision of three-dimensional surgical movements has improved substantially [5,6]. As a result, surgeons and patients now have the ability to visualize and achieve facial cosmetic changes that were once considered unattainable [7]. This progress in orthognathic surgery planning has led to faster and more accurate procedures, thereby enhancing safety, efficiency, and reducing complications [8,9]bisagittal split osteotomy, with or without genioplasty. All subjects had to have preoperative (T0.

In recent times, a novel tool, known as orthodontic aligners, has been introduced as an adjunct to orthognathic surgery procedures. However, due to its novelty, many orthodontists and maxillofacial surgeons are not yet familiar with its implementation. Consequently, technical challenges may arise during its utilization. Nevertheless, several studies have reported successful orthodontic aligner usage in preparation for orthognathic surgery, without compromising clinical outcomes [10,11]. Despite these affirmations, concerns remain regarding the potential complications or negative consequences that may arise from improper planning [12].

The number of patients and professionals seeking or considering treatment with orthodontic aligners has significantly increased [13,14]. Therefore, the objective of this study is to conduct a retrospective survey assessing the expertise of maxillofacial surgeons regarding orthodontic aligners. This will facilitate a comprehensive discussion on the feasibility and applicability of utilizing clear aligners in orthognathic surgery, with the goal of achieving enhanced surgical safety and superior outcomes.

Main Points;

- While orthodontic aligners offer advantages such as patient convenience and improved hygiene, not all cases are suitable for orthognathic surgery prepared with aligners.
- The study highlights both the benefits and challenges associated with aligner usage, including postoperative occlusal stability, limitations of intermaxillary blocks, and difficulties in using elastic bands.
- Importantly, our research underscores the need to address these challenges to enhance the effectiveness and outcomes of orthognathic surgery with aligners.

MATERIALS AND METHODS

A study design used an online survey questionnaire consisting of nine single-choice and descriptive questions was designed and implemented on Google Forms (Google, Menlo Park, CA, USA). The appropriateness of the questions was debated between the authors and some ideas from other experienced surgeons. The link to the online questionnaire was then sent via e-mail and smartphone message to a variety of OMS surgeons worldwide, with a brief explanation of the purpose of the study. The e-mail addresses were searched on ResearchGate (www.researchgate.com), a social media of researchers.

The online questionnaire was designed to be rapid, anonymous and non-exhaustive to decrease non-responsiveness. Participants started the survey by clicking on the link provided in the e-mail. The questionnaire was created and was available in three different languages (English, Portuguese and Spanish). The link opened the survey directly, and participants were not required to create an account or enter personal information to complete the survey. The target sample of surgeons was determined by the suspicion of having sufficient knowledge and experience in orthognathic surgery. The questionnaire consisted of four personal questions and five research-specific questions (Table 1). As a form of content validity, a pretest survey was sent to 16 residents and postgraduates.

Statistical Analysis

Fischer exact test was performed with RStudio ® (RStudio, GNU GPL) and was considered significant with a 95% confidence interval. Descriptive analytic statistics were performed on most available data. The study met the criteria for exemption according to the institutional review board.

RESULTS

A total of 396 online questionnaires were sent, 277 to Brazilian and 119 to worldwide surgeons. A total of 92 responses were collected during a 2-month period. Respondents were 76 male (82.61%) and 16 female (17.39%) maxillofacial surgeons. The majority was in the 31 to 40 age range (36.96%) followed by 41 to 50 (36.96%) (Figure 1). The geographic data are shown in Figure 2. Majority of maxillofacial surgeons can be considered as experts, with more than 10 years of experience in orthognathic surgery (Figure 3). Most surgeons (n = 50) have performed at least one orthognathic surgery using orthodontic aligners treatment (54.34%).

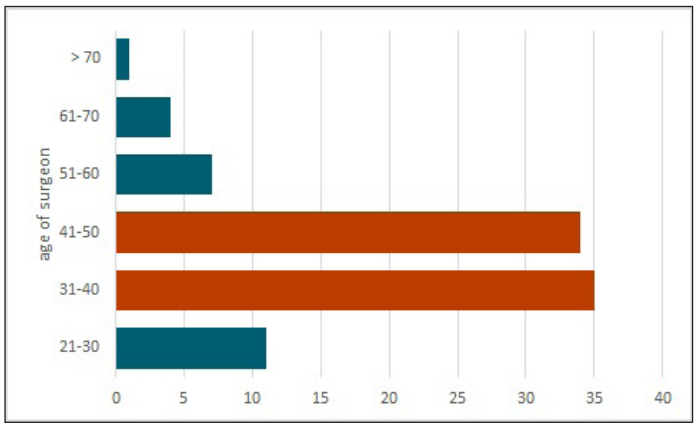

Figure 1. Prevalence of maxillofacial surgeons according to age range

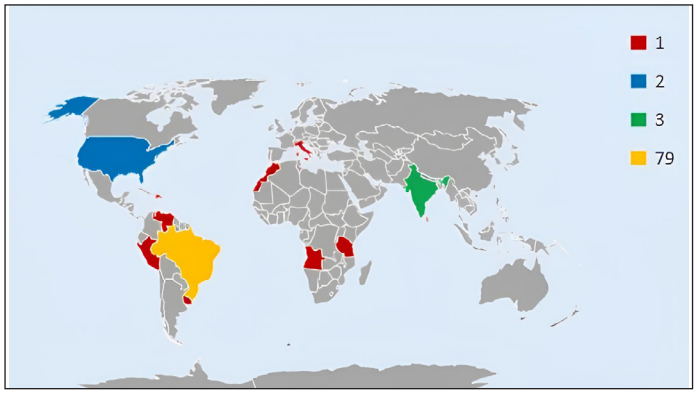

Figure 2. World map of included answers

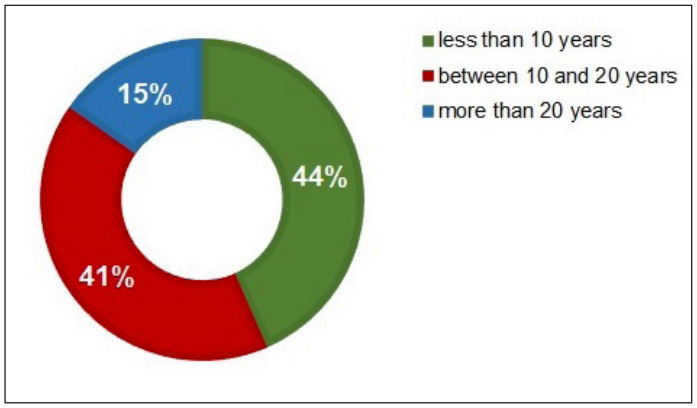

Figure 3. Maxillofacial surgeons' expertise on orthognathic surgery

Responses of these 50 surgeons with positive answers on orthodontic aligners experience were assessed for obstacles, advantages, and disadvantages. It resulted in a low full response rate (12.62%), and this can be explained due to massive number of online surveys performed during COVID-19 pandemics [15]. Surgeons have preferred to use intermaxillary screws (60.87%) rather than using hooks adapted to conventional orthodontic appliances (32.61%) or buttons/attachments on teeth (38.04%). Some surgeons prefer to use more than a single method (n = 29).

Regarding obstacles, advantages, or disadvantages in performing orthognathic surgery treated with orthodontic aligners, Table 2 summarizes the results. Maxillofacial surgeons treated obstacles as a disadvantage. Some surgeons reported advantages (n = 8) and disadvantages (n = 15) but did not explain them. Some recommendations were given to maxillofacial surgeons in Table 3.

A comparison was made between the number of reported advantages and disadvantages. A Fisher exact test resulted orthodontic aligners had more disadvantages than advantages (p = 0.0504), but this result was not considered statistically significant.

DISCUSSION

The objective of this study was to assess the firsthand experience of maxillofacial surgeons in utilizing orthodontic aligners for orthognathic surgery preparation, with a specific focus on highlighting the advantages and disadvantages associated with this approach. Additionally, the study aimed to explore potential obstacles that may arise during the preoperative, intraoperative, and postoperative phases, along with strategies for effectively managing them.

Orthodontic aligners, also known as clear aligners, emerged in the 1990s and gained significant popularity from 2001 onwards [13]. These aligners have revolutionized the field of orthodontic treatment, leading to a substantial increase in their utilization [16,17]. Orthodontic treatment combined with orthognathic surgery is frequently necessary to effectively manage patients suffering from severe craniofacial deformities. Brackets and wires are conventionally utilized for intraoperative splint stabilization in conventional orthognathic surgery, but such an approach is not applicable for patients undergoing treatment using clear aligners (the Invisalign system. Despite a noticeable upward trend in the number of publications related to orthodontic aligners, there is limited research evaluating the experience of maxillofacial surgeons in utilizing them for orthognathic surgery preparation [14]. Nevertheless, numerous studies have reported various benefits, and both patients and orthodontists have expressed high levels of satisfaction with this treatment modality [14,17] but such an approach is not applicable for patients undergoing

Table 1. Questions of the online questionnaire

Question 1	What is your gender?
Question 2	What is your age range?
Question 3	In which country is your main professional practice based?
Question 4	How many years have you been performing orthognathic surgery?
Question 5	Have you ever operated an orthognathic surgery treated with orthodontic aligners?
Question 6	For the surgery, which devices did you use for intermaxillary fixation? • Hooks adapted on conventional orthodontic appliances • Intermaxillary screws • Buttons or attachments on teeth
Question 7	Was there any surgical obstacle?
Question 8	Do you think there is any advantage or disadvantage in performing orthognathic with orthodontic aligner?
Question 9	Any recommendation to other surgeons before performing orthognathic surgery with orthodontic aligners?

Table 2. Advantages and disadvantages in performing orthognathic surgery with orthodontic aligners

Advantages		Disadvantages	
None	1	None	4
Patient friendly	13	Lack of postoperative occlusal stability	16
Better hygiene	9	Intermaxillary block less efficient	14
Occlusal previsibility	4	Difficulty in using elastic bands	12
Faster orthodontic treatment	3	Limitation in performing orthodontically complex cases, i.e. maxillary segmentation	10
		Switch to conventional preoperative appliance	5
		Surgery cost	2
		Lack of digital planning tools	1

Table 3. Pre, trans and postoperative recommendations to maxillofacial surgeons

Precise conference of orthodontic preparation before scheduling surgery (intercuspation and occlusal stability)	23
Replacement of the aligners with brackets before surgery	8
Case selection	6
The use of elastics in the postoperative period must be accompanied by a lingual retainer to avoid vertical tooth movements	4
Avoidance of maxillary segmentation	3
Care in wearing aligners in postoperative period	2
Use of elastic chain intermaxillary block	1
Wait new studies	1

treatment using clear aligners (the Invisalign system. However, it should be noted that while there is considerable interest and positive feedback, financial constraints have hindered some maxillofacial surgeons from operating on cases prepared with aligners. Consequently, uncertainties persist when orthodontic preparation is required for orthognathic surgery. It is essential for researchers to exercise caution when conducting online surveys, particularly in the context of the COVID-19 pandemic, as the response rates may not meet expectations due to survey fatigue and the overwhelming number of surveys being administered [15]. Therefore, it is advisable to avoid extensive and time-consuming online surveys to ensure meaningful and reliable data collection.

The utilization of orthodontic aligners in preparation for orthognathic surgery has emerged as a contemporary concern, particularly in complex cases. One notable limitation of aligners compared to conventional orthodontic treatment is the absence of dynamic mechanics, resulting in differential stability [13,18,19] Aligners are primarily effective for tooth alignment, as their name suggests, but may exhibit imprecisions such as lingual displacement of molars, intrusion of lower molars, buccal torque of upper incisors, and rotational movements [19–21]. Maxillofacial surgeons must ensure that appropriate leveling and occlusion are achieved through orthodontic preparation. Currently, there is no consensus in the literature regarding the superior effectiveness or efficacy of orthodontic aligners [10,22,23] Complications such as inadequate alignment, damage to intermaxillary fixation screws, and incorrect positioning of the occlusal plane may arise.

Despite the clear disadvantages for surgeons, they must acknowledge and embrace the increasing demand for orthodontic aligners from patients seeking enhanced comfort, particularly in terms of periodontal health and overall quality of life [14,17,24] The proliferation of social media videos and marketing campaigns has significantly contributed to the rising number of patients opting for orthodontic aligner treatment.

The preference for intermaxillary screws over hooks adapted to conventional orthodontic appliances or buttons/attachments on teeth among surgeons indicates a clear inclination towards the use of screws for intermaxillary fixation during orthognathic surgery. This finding suggests that screws offer certain advantages or perceived benefits that make them the preferred choice in most cases. Further exploration of these advantages and their impact on surgical outcomes would provide valuable insights into the reasons behind this preference. Additionally, the finding that some surgeons opt for multiple methods suggests a personalized approach, where the choice of technique may depend on the specific requirements of each case or surgeon preference.

The reported advantages include patient-friendliness, improved hygiene, occlusal previsibility, and faster orthodontic treatment. These benefits align with the patients' perspective and their desire for more comfortable and convenient treatment options. However, it is important to note that the advantages mentioned were reported by a smaller number of surgeons compared to the disadvantages. The reported disadvantages include a lack of postoperative occlusal stability, less efficiency of intermaxillary blocks, difficulties in using elastic bands, limitations in performing orthodontically complex cases (such as maxillary segmentation), the need to switch to conventional preoperative appliances, and surgery cost. These findings highlight the existing challenges and limitations associated with orthodontic aligner usage in orthognathic surgery.

Collaboration and discussion with orthodontic aligner companies could help address some of the reported issues. The use of elastics plays a critical role in maintaining postoperative stability by leveraging muscle strength. The development of devices that facilitate the proper utilization of elastics could significantly aid in this regard. Similarly, exploring alternatives to conventional orthodontic appliances and intermaxillary blocks, such as custom splints, may prove beneficial [25]. Once these challenges are overcome, the need for transitioning from aligners to conventional appliances in the preoperative phase could be minimized.

Unfortunately, the novelty of orthodontic aligners and their dependence on digital technology have resulted in higher costs for orthognathic surgery. This financial barrier restricts the widespread adoption of orthognathic surgery prepared with orthodontic aligners in certain regions.

Careful case selection is imperative [18,21]. Not all patients are suitable candidates for orthodontic aligners, particularly in the context of orthognathic surgery preparation. The selection and management of orthodontic appliances play a crucial role in achieving positive outcomes [12]. Our survey findings indicate that maxillary segmentation should be approached

cautiously due to the limited efficiency in managing tooth root distalization compared to conventional orthodontics. Both patients and surgeons should be aware about the importance of precise conference of orthodontic preparation before scheduling surgery is emphasized, particularly focusing on intercuspation and occlusal stability.

While a randomized clinical trial would provide a higher level of evidence and more reliable data, it would be limited to the experience of a single surgical team. Online research, on the other hand, offers valuable and up-to-date information from various surgeons on the subject.

Limitations

This survey shares common limitations with other studies of its kind. The questions were not specifically designed to address the broader knowledge on the topic but rather aimed to capture the overall experience of surgeons. The low response rate does not diminish the risk of type 2 error (false negative) and prevents cross-referencing of answers regarding experience, training duration, number of surgeries performed, and the described advantages and obstacles. Future studies may corroborate these findings or shed light on the knowledge gaps surrounding treatment possibilities and functionalities of orthodontic aligners. Furthermore, investigating different brands of orthodontic aligners and assessing the advantages and disadvantages of each is also a topic worth exploring.

CONCLUSION

The results of the present study have shown that respondent surgeons agree that orthognathic surgery prepared with orthodontic aligners is not suitable for all cases such as maxillary segmentation. The preference for intermaxillary screws among surgeons for orthognathic surgery fixation indicates their perceived advantages and benefits. The utilization of multiple methods also suggests a personalized approach based on case-specific requirements and surgeon preferences. The reported advantages of orthodontic aligners, including patient-friendliness, improved hygiene, occlusal previsibility, and faster orthodontic treatment, align with patient expectations for comfort and convenience. However, the smaller number of surgeons reporting advantages compared to disadvantages highlights the existing challenges and limitations associated with aligner usage, such as postoperative occlusal stability, efficiency of intermaxillary blocks, and difficulties with elastic band usage. Addressing these challenges will be essential for enhancing the efficacy and outcomes of orthognathic surgery with orthodontic aligners.

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Original Research

Academic and Online Attention to Palliative Care: A Bibliometric and Altmetric Perspective

Bahar Bektan Kanat

Division of Geriatric Medicine, Department of Internal Medicine, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey

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Correspondence
Bahar Bektan Kanat, MD
Address: Division of Geriatric Medicine, Department of Internal Medicine, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey
E-mail: baharbektan@gmail.com

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ABSTRACT

Objective: With a combined bibliometric and altmetric study, we aimed to provide a visually detailed perspective on palliative care, which is attracting increasing attention from academia and society. We also evaluated the relationship between supporting and contrasting citation counts and the altmetric attention score (AAS) for the first time in the literature.

Methods: Web of Science (WoS) database and Altmetric.com website was used to create Top100 (T100) citation and altmetric lists. Supporting and contrasting citations were found using Scite.ai database. Articles in both lists, published between 1975-2021, were analyzed in terms of study type, topic, first author, publication year, citation count, AAS, Scite score, and supporting and contrasting citation counts. Impact factor (IF), quartile of journal and journal citation indicator (JCI) were also examined.

Results: A search of "Palliative care" in WoS yielded a total of 50.674 articles. A significant correlation was found between AAS and citation counts (p=0.001, r=0.328) in T100 citation list, and AAS and contrasting citations in T100 altmetric list (p=0,024, r=0,225). There was no statistically significant difference between IF, JCI and Q categories in both lists. The topic "PC for non-oncological diseases" were at the top of both lists. The USA, UK and Canada were countries with the most articles in T100 citation list.

Conclusions: Palliative care articles that attract the attention of the academia also resonate on social media. Since AAS can be manipulated, it would be beneficial to use altmetric analysis in combination with bibliometric analysis rather than alone to formulate new policies on palliative care.

Keywords : Palliative care, bibliometric analysis, altmetric analysis, Scite

INTRODUCTION

Palliative care is specialized medical care aimed at reducing symptoms such as pain and improving quality of life in patients suffering from cancer, major organ failure, end-stage chronic diseases, severe burns and extreme frailty of old age. The World Health Organization (WHO) reported that palliative care may be needed at all levels of care and 40 million people need palliative care each year [1]. Palliative care is carried out by a team formed by doctors, nurses and other health professionals about the patient's health problems and the care process is planned by the needs of the patient. In addition to the benefits for patients and caregivers, the benefits for the government due to cost savings

have made palliative care one of the most rapidly growing fields of health care [2]. This is not surprising because of the aging world, the prolongation of life expectancy with treatments for various diseases, changes in health policies and the awareness of societies. A better understanding of current research trends can further reveal global approaches, needs and challenges in palliative care.

Bibliometric analysis uses citation rates to evaluate the performance of a scientific output. This method enables researchers to access valuable articles that shed light on science in their field [3]. There are many studies on this analysis in medicine [4-6]. Today, in addition to bibliometric analyzes that show the place of articles in academia, altmetric analyses that show their place in social media are also frequently encountered. The altmetric attention score (AAS) represents the power of the articles in social media [7]. Considering how big a place social media occupies in our lives, it should come as no surprise that the popularity of altmetric analysis is increasing day by day.

The concept of citation markers, first discussed by Eugene Garfield [8] in 1964, was developed by Josh Nicholson and Yuri Lazebnik [9], and the Scite.ai database was created in 2014 [8,9]. Scite is a deep learning platform that helps researchers better evaluate scientific articles. In addition to the citation counts, Scite shows how an article is cited by analyzing whether it provides evidence that supports or contradicts the cited claim [10].

In this study, scientific outputs related to palliative care at the global level were evaluated, bibliometric and altmetric analysis of publications was performed with the aim of policy-making, providing useful information for new research topics and reviewing scientific research trends of both academia and society. In addition, we aimed to evaluate the relationship between bibliometric analysis and altmetric analysis, and also the relationship between supporting and contrasting citation statements and altmetric attention score in our study.

Main Points;

- Although citation count and Altmetric attention score are different concepts, valuable articles on palliative care in academia also resonate on social media.
- The article titled 'Early palliative care in patients with metastatic non-small cell lung cancer' attracted the most attention from both the academic community and the public.
- The countries with the highest number of articles on palliative care were the USA, England and Canada.

MATERIALS AND METHODS

We searched all the articles, published between 1975-2021, related to the keyword "Palliative care" from Thomson Reuters Web of Science (WoS) in all databases (Philadelphia, Pennsylvania, USA) on March 4, 2021. WoS database shows all articles containing the keyword in title, abstract or keywords. The T100 citation list was created by two researchers by reading all articles and excluding articles not primarily related to palliative care. The T100 citation list was prepared according to the topic of the article, type of the article, the first author, year of publication, the number of citations, average citations per year (AcPY). Impact factor (IF), Quartile (Q) rankings and journal citation indicator (JCI) values of the journals for the year 2021 were used. JCI value is a new journal citation impact measurement that shows the average category-normalized citation effect of articles published in the last 3 years in line with data from the Web of Science [11]. In addition, a network visualization map was used for the keywords, countries and institutions of the T100 citation list.

On the same day with the WoS scan, a search for "Palliative care" was performed on Altmetric.com website and 100 articles with the highest altmetric attention score (AAS) were noted. AAS is the quantity of attention that an article has received. AAS is presented in the center of the altmetric donut. The colors of the donut represent sources of attention and the area of colors shows the contribution of the source to the AAS. News (has the highest coefficient), blogs, public policy documents, patents, post-publication peer-review platforms, Open Syllabus Project, research highlights, Wikipedia, Twitter, Facebook, Google+, Linkedln, Q&A, Reddit, Sin Weibo, Syllabi, Youtube and Pinterest are the contributors of the AAS [12, 13]. In addition, the AAS of the T100 cited articles were obtained from Altmetric.com website, and citation counts of the T100 altmetric list were obtained from the WoS website on the same date. The AAS value of articles that could not be found on the Altmetric.com website was assumed to be zero.

Apart from these, we scanned all articles in both the T100 bibliometric and T100 altmetric lists in the Scite.ai website for March 2021. We recorded the total scite score, supporting and contrasting citation statements for each article. Scite AI is

a Brooklyn-based startup designed to make a difference in the way researchers discover scientific papers. The Smart Citations feature shows whether citations to the article provide supporting or contrasting evidence. This allows us to approach the article from a more objective point of view. It also provides appropriate references and data when drafting articles. There are also some limitations to the application. There may be a small number of journals or publications that it does not cover. Also, over-reliance on the database to categorize supporting or opposing evidence can lead to bias. Nevertheless, despite all this, the qualitative analysis it provides is a great convenience for researchers.

Statistical Analysis

Categorical variables were defined as median (minimum-maximum). Since the data was not normally distributed, Mann-Whitney U test was used to compare the differences between two groups; and Kruskal-Wallis test was used to compare three or more groups. Spearman correlation analysis was performed to evaluate the correlation between citation count, AAS, supporting and contrasting citation statements in T100 citation and altmetric lists. $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Statistics Version 25.0 software (IBM, Chicago, IL).

RESULTS

We found 50.674 articles by searching "Palliative care" in the Web of Science database. Top cited 100 articles about palliative care is given in Supplement 1; with the number of citations, AcPY, AAS, altmetric score donut, scite score, supporting and contrasting citation statement count, first author and year of publication. The median citation count of the top 100 cited articles was 422,5 (IQR, 339,2-585,5), while the median Scite score was 500 (IQR, 423-723,5) and AAS was 28 (IQR, 10-90). The article titled "Early palliative care in patients with metastatic non-small cell lung cancer" by Temel JS [14] was at the top of both lists (n=3724, AAS=1401) (rank 1 in Supplement 1 and Supplement 2). The article also had the highest scite score with 4407 in both lists, and there were 66 supporting and 12 contrasting citation statements [14]. The highest altmetric score (n=1461) in the T100 citation list belonged to the fourth most cited article (n=2324) entitled "CDC guideline for prescribing opioids for chronic pain-United States 2016" by Dowell D et al (rank 4 in Supplement 1) [15]. The Spearman correlation analysis was used to define the correlation between citation count, AAS and scite scores (supporting, contrasting) of the T100 citation and T100 altmetric articles. While a significant correlation was found between AAS and citation ($p=0.001$, $r=0.328$) in addition to the significant correlation between AAS and supporting citation statement count on scite ($p=0.011$, $r=0.255$), no statistically significant correlation was found between AAS and contrasting citation statements in T100 citation list ($p=0.347$, $r=0.96$). For T100 altmetric list, no significant correlation was found in terms of AAS and citation counts ($p=0.110$, $r=0.161$), and AAS and supporting citation statements ($p=0.888$, $r=0.014$) but there was a significant correlation between AAS and contrasting citation statement counts ($p=0.024$, $r=0.025$). In terms of AcPY, there was a significant correlation between AcPY and citation count and AAS ($p<0.001$, $r=0.607$; $p<0.001$, $r=0.747$; respectively).

Top100 altmetric list is given in Supplement 2 including 100 articles about palliative care with the highest AAS, as well as altmetric score donut, the number of citations, scite score, supporting and contrasting citation statement count, first author and year of publication of the articles. The median citation count of the T100 altmetric articles was 44,5 (IQR 6.-95,7), the median for the scite score was 52 (IQR, 10-132) and AAS was 229,5 (IQR 183,2-391). The article "Early palliative care for patients with advanced cancer: a cluster-randomized controlled trial" published in the Lancet in 2014, ranked 48th in the T100 altmetric list with 241 AAS, was in the second rank in terms of citation and scite scores (n=750, n=1056; respectively) [16]. This article was ranked 11 in the T100 citation list. No correlation was found between the citation count, supporting citation statements and AAS of the T100 altmetric articles, according to Spearman correlation analysis ($p=0.110$, $r=0.161$; $p=0.888$, $r=0.14$; respectively) while there was a significant correlation between AAS and contrasting citation statements ($p=0.024$, $r=0.225$).

Journal of Clinical Oncology (n=11), JAMA-Journal of the American Medical Association (n=9) and Journal of Pain & Symptom Management (n=6) were the journals with the highest number of articles in the T100 citation list. In the T100 altmetric list, the journals with the highest number of articles were Palliative Medicine (n=15), JAMA-Journal of the American Medical Association (n=8) and British Medical Journal (n=7). The median IF and JCI values of the journals in which the articles in the top 100 citation list were published were 21.25 (IQR 6.5-69.5) and 3.77 (IQR 1.36-8.23), while those in the top 100 altmetric list were 10.42 (IQR 5.57-85.77) and 2,07 (IQR 1.24-7.45), respectively. IF and JCI values of journals were summed up for each list and divided by the number of articles.

There was no statistically significant difference between IF, JCI and Q categories in both lists (p=0.079; p=0.131 and p=0.574; respectively). Interestingly 'Journal of palliative care', which is Q4 according to the Scimago Journal and Country Rank category, was one of the journals in the T100 citation list. Journals with two or more articles in both lists, article counts, IF, JCI values and Q categories are given in Table 1.

Table 1. Journals with two or more articles in T100 citation and altmetric lists

Rank and Journal	The Number of Articles	Impact Factor*	Quartile in Category**	Journal Citation Indicator***
Top 100 citation list				
1.Journal of Clinical Oncology	11	50.739	Q1	5.64
2. JAMA-Journal of the American Medical Association	9	157.375	Q1	10.46
3. Journal of Pain&Symptom Management	6	5.576	Q1	1.42
4. New England Journal of Medicine	5	176.082	Q1	22.47
5. British Medical Journal	5	96.216	Q1	7.45
6. Lancet Oncology	4	54.433	Q1	8.50
7. Archives of Internal Medicine	4	17.333	Q1	
8. Palliative Medicine	4	5.713	Q1	1.24
9. Lancet	3	202.731	Q1	21.87
10. CA-A Cancer Journal for Clinicians	2	286.13	Q1	68.74
11. Annals of Internal Medicine	2	51.598	Q1	6.01
12. Circulation	2	39.922	Q1	6.31
13. Cochrane Database of Systematic Reviews	2	11.874	Q1	1.33
14. Critical Care Medicine	2	9.296	Q1	1.47
15. British Journal of Cancer	2	9.082	Q1	1.41
16. Pain	2	7.926	Q1	1.77
17. Journal of the American Geriatrics Society	2	7.538	Q1	1.62
18. Journal of Palliative Medicine	2	2.947	Q3	0.76
Top 100 altmetric list				
1. Palliative Medicine	15	5.713	Q1	1.24
2. JAMA-Journal of the American Medical Association	8	157.375	Q1	10.46
3. British Medical Journal	7	96.216	Q1	7.45
4. JAMA Oncology	6	33.012	Q1	5.20
5. Journal of Pain&Symptom Management	6	5.576	Q1	1.42
6. BMJ Supportive & Palliative Care	6	4.633	Q1	0.89
7. Lancet	5	202.731	Q1	21.87
8. Journal of Palliative Medicine	5	2.947	Q3	0.76
9. New England Journal of Medicine	4	176.082	Q1	22.47
10. Journal of Clinical Oncology	4	50.739	Q1	5.64
11. Lancet Oncology	3	54.433	Q1	8.50
12. Canadian Medical Association Journal	3	16.876	Q1	2.07
13. Health Affairs	3	9.048	Q1	2.77
14. JAMA Internal Medicine	2	44.424	Q1	4.86
15. Cochrane Database of Systematic Reviews	2	11.874	Q1	1.33
16. Annals of Emergency Medicine	2	6.762	Q1	2.60
17. Oncologist	2	5.837	Q2	1.03
18. American Journal of Hospice & Palliative Care	2	2.09	Q4	0.64

* 2021 Journal Citation Reports (Clarivate Analytics)
** 2021 Scimago Journal and Country Rank
***2021 Clarivate Analytics

Most frequent year of publication of articles in T 100 citation list was 2007 with 8 articles, and it was seen that there were articles belonging to almost every year between 1992 and 2017. While 2016 was the year in which the most articles were published in T100 altmetric list with 19 articles, 2017 and 2018 followed it with 17 articles each.

When we grouped the articles according to study types, we found that the most common study type was original article in both lists (n=43, n=55; respectively). According to article types; while there was no difference between citation counts in the T100 citation list (p=0.486), there was a significant difference between AAS, supporting citation statements and contrasting citation statements (p=0.028, p=0.001, p<0.001). On the other hand, there was no significant difference between the number of citations, AAS, supporting and contrasting citation statement counts according to article types in the T100 altmetric list (p = 0.611, p=0.382, p=0.361, p=0.356; respectively). Study types of the lists and statistical analyzes are given in Table 2.

Table 2. Study types of the articles in top 100 citation and altmetric list

Study Type	Number of articles	Citations, median (IQR)	p value	AAS, median (IQR)	p value	Scite Supporting, median (IQR)	p value	Scite contrasting, median (IQR)	p value
Top 100 citation list	100	422 (339-585)		28 (10-90)					
Original scientific paper	43	423 (334-553)	0.486	19 (4-62)	**0.028**	12 (5-19)	1	3 (1-4)	**<0.001**
Review	26	483 (337-629)		28 (16-176)		6 (2-10)		0 (0-0)	
Guidelines and advisory documents	18	411 (345-601)		32 (17-85)		5 (4-7)		0 (0-0)	
Systematic reviews and meta-analyses	13	449 (374-774)		69 (23-413)		15 (7-23)		3 (1-4)	
Top 100 altmetric list	**100**	44 (6-95)		229 (183-391)					
Original scientific paper	55	38 (6-97)	0.611	224 (176-358)	0.382	1 (0-4)	0.361	0 (0-1)	0.356
Review	28	48 (9-129)		245 (192-427)		0 (0-0)		0 (0-0)	
Systematic reviews and meta-analyses	11	24 (4-71)		204 (179-381)		1 (0-3)		0 (0-0)	
Guidelines and advisory documents	6	81 (20-348)		339 (185-665)		1 (1-5)		0 (0-0)	

AAS, Altmetric Attention Score

The articles in both lists were divided into 6 groups according to their topics: palliative care for oncology patients, palliative care for non-oncological diseases, pain, cost, healthcare workers-caregivers and Covid-19. The most common topic was 'palliative care for non-oncological diseases' in T100 citation and altmetric lists (n=39, n = 49; respectively) and the second was 'palliative care for oncology patients' in both lists (n =36, n=24; respectively). According to the article topics, there was no difference between the groups in terms of the citation counts, AAS and supporting citation statement counts in the T100 citation list (p=0.063, p=0.772, p=0.192; respectively), but there was a statistically significant difference in contrasting citation statement counts (p=0.003). For T100 altmetric list no statistically significant difference was found in terms of both AAS and contrasting citation statement counts (p=0.263, p=0.080; respectively) but there was a statistically significant difference in citation and supporting citation statement counts (p=0.014, p<0.001; respectively). See Table 3 for the topics of articles in both lists and statistical analyzes. In addition, while there are 4 articles about children in the T100 citation list, no articles for that age group were found in the T100 altmetric list.

The most commonly used keywords in the T100 citation list were found to be palliative care, terminal care and cancer. A network visualization cluster map for keyword analysis about palliative care for the top 100 cited articles is given in Figure 1. The majority of publications in the T100 citation list have come from the United States, England and Canada. Countries of the authors and network of countries are given in Figure 2. The most contributing institutions in T100 citation list were Harvard University, Memorial Sloan Kettering Cancer Center, University of Washington and King's College London, respectively. For the correlation and clusters of contributing institutions in the T100 citation list see Figure 3.

Table 3. Topics of the top 100 citation and altmetric list

Topic	Number of articles	Citations, median (IQR)	P value	AAS, median (IQR)	P value	Scite supporting, median (IQR)	P value	Scite contrasting, median (IQR)	p value
Top 100 citation list	100	422 (339-585)		28 (10-90)		8 (4-16)		1 (0-3)	
PC for non-oncological diseases	39	378 (334-487)	0.063	27 (12-62)	0.772	7 (4-15)	0,192	0 (0-2)	**0.003**
PC for oncology patients	36	516 (354-692)		40 (9-93)		10 (4-24)		2 (1-4)	
Pain	13	389 (339-774)		25 (4-281)		6 (2-8)		0 (0-2)	
Healthcare workers, care givers	10	453 (376-549)		19 (9-220)		10 (5-22)		3 (1-5)	
Cost	2	488 (484-)		72 (70-)		16 (14-)		3 (0-)	
Top 100 altmetric list	100	44 (6-96)		229 (183-391)		1 (0-3)		0 (0-0)	
PC for non-oncological diseases	49	20 (6-64)	**0.014**	225 (181-391)	0.263	0 (0-1)	**<0.001**	0 (0-0)	0.080
PC for oncology patients	24	89 (13-200)		212 (182-293)		2 (0-9)		0 (0-0)	
Healthcare workers, care givers	11	97 (6-209)		184 (170-358)		2 (1-8)		0 (0-1)	
Pain	6	3 (2-70)		387 (245-582)		0 (0-1)		0 (0-0)	
Covid-19	6	22 (13-50)		324 (194-485)		0 (0-0)		0 (0-2)	
Cost	4	103 (65-196)		205 (179-806)		4 (2-5)		1 (0-2)	

IQR, Interquartile intervals; **AAS,** Altmetric Attention Score; **PC**, Palliative care

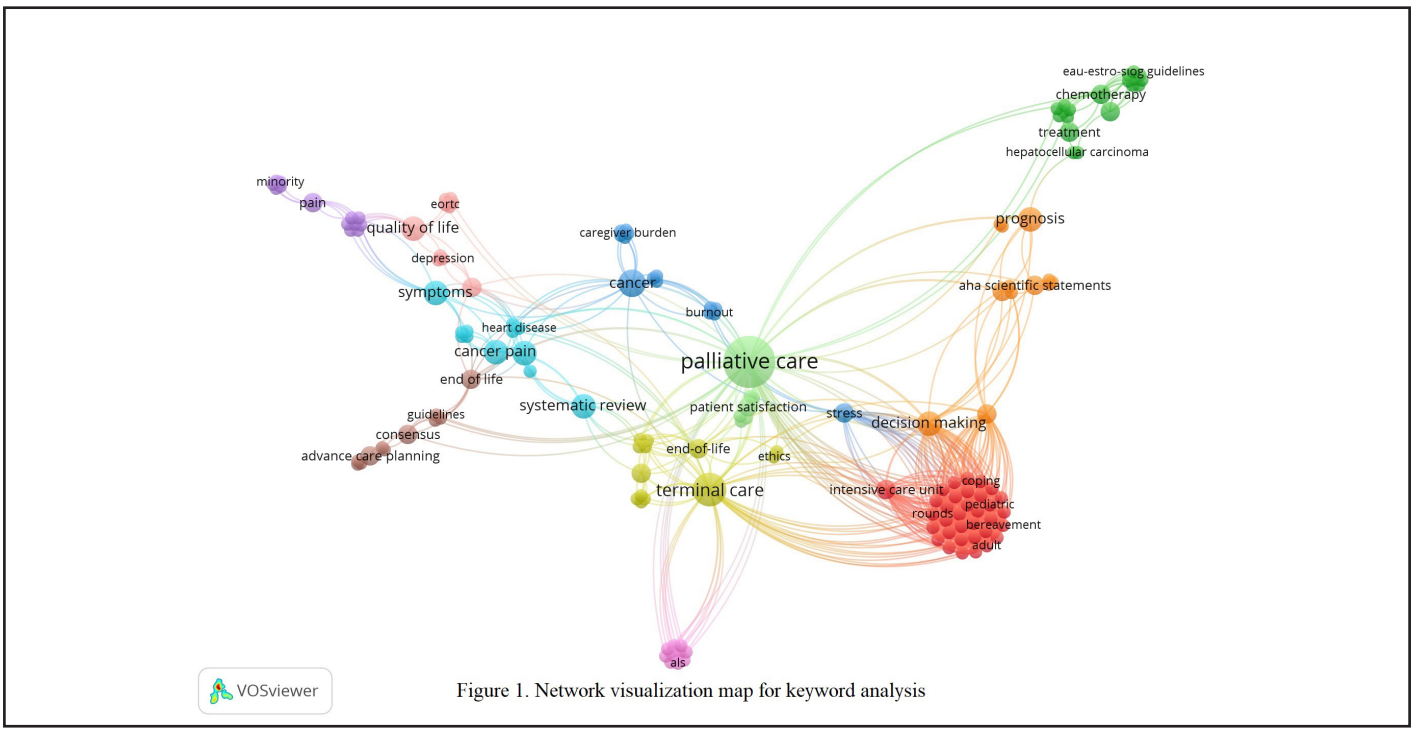

Figure 1. Network visualization map for keyword analysis

Figure 1. Network visualization map for keyword analysis

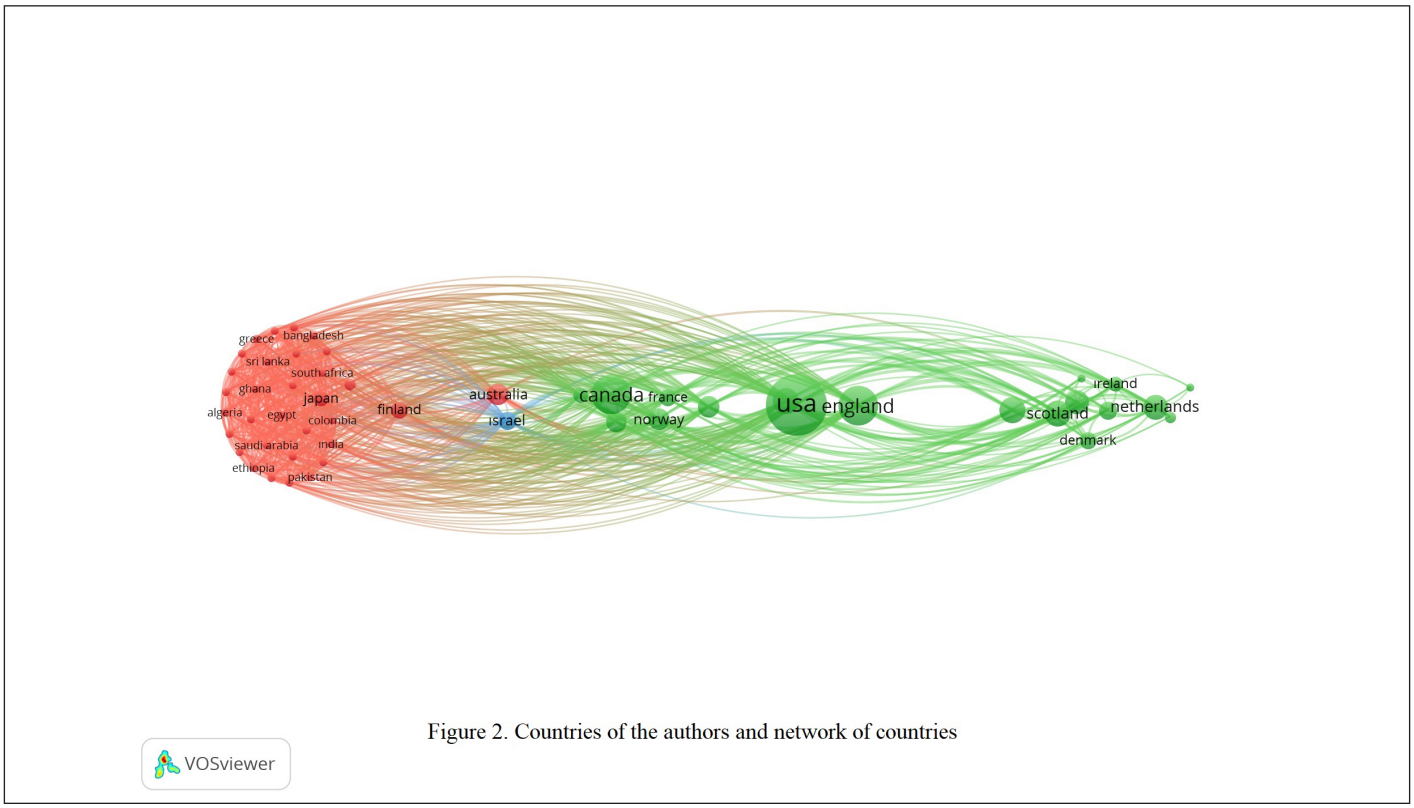

Figure 2. Countries of the authors and network of countries

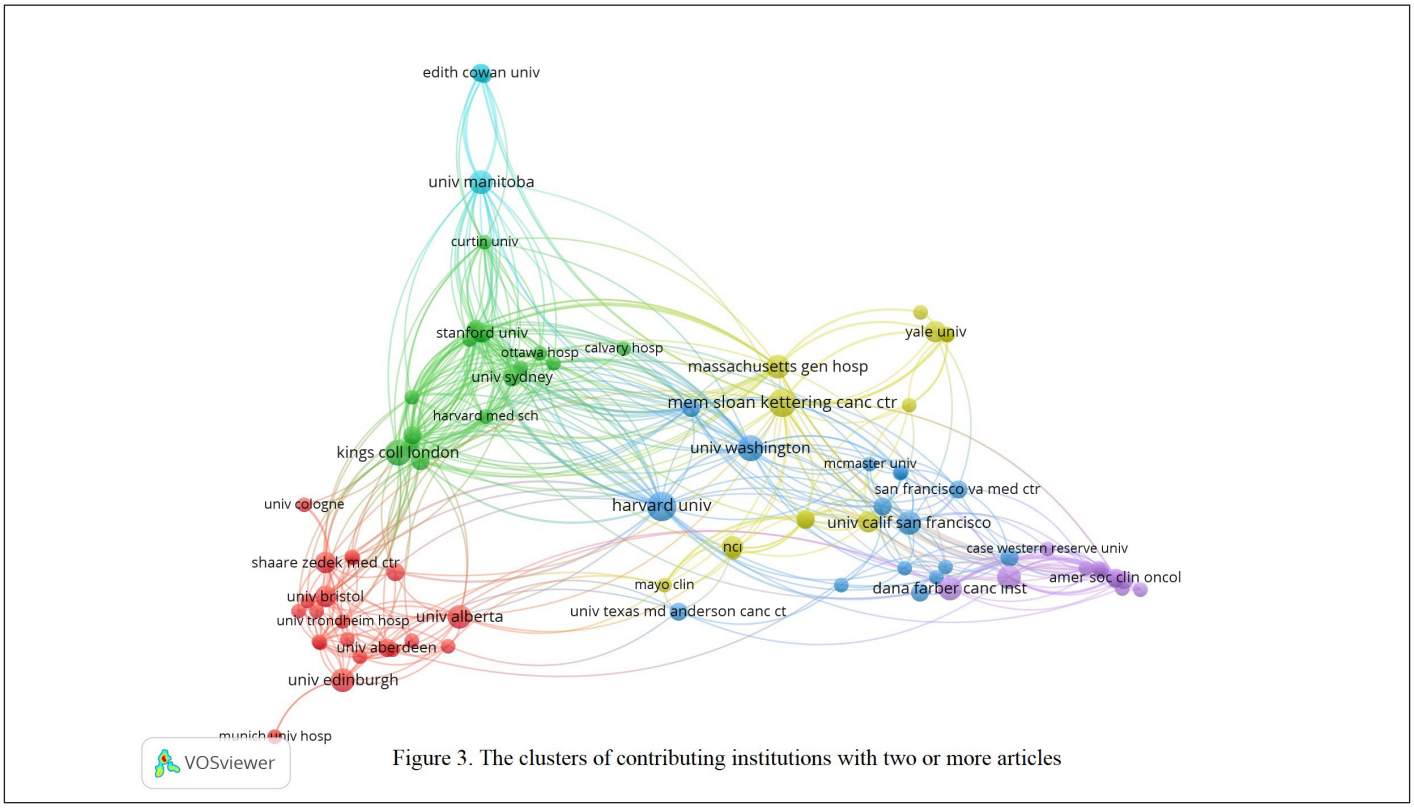

Figure 3. The clusters of contributing institutions with two or more articles

DISCUSSION

There are bibliometric studies on palliative care in the literature. However, as far as we know, our study is the first and only study to date that compares bibliometric analysis and altmetric analysis in this field, and also evaluates these three axes together by examining the relationship between supporting and contrasting citation counts and altmetric attention score. Our study investigated the 100 most cited articles in the academic community and the 100 most discussed articles on social media about palliative care, and revealed that although the number of citations and AAS are different concepts, the articles that have an important place in the academy also aroused some repercussions in the social media. Unlike existing studies, our study, in which we included the concept of JCI in addition to scite scores, is the most comprehensive study in this field.

"Early palliative care in patients with metastatic non-small cell lung cancer", the article at the top of both the T100 citation and T100 altmetric lists, was a randomized controlled trial examining the impact of initiating palliative care early after diagnosis on self-reported outcomes and end-of-life care in patients with newly diagnosed disease The study showed that early palliative care in patients with non-small cell metastatic lung cancer leads to significant improvements in both quality of life and mood, in addition, patients who receive early palliative care need less aggressive care at the end of their lives and have a longer survival [14]. "Definition and classification of cancer cachexia: an international consensus", which was ranked second in the T100 citation list with 2020 citations and 2385 scite score (43 supporting and 4 contrasting citation statements) had only 47 AAS. In this consensus report for experts, cancer cachexia was defined and its pathophysiology, classification and clinical management were described. Cancer cachexia has been defined as a multifactorial syndrome characterized by loss of skeletal muscle mass leading to progressive functional impairment. The accepted diagnostic criteria for cachexia was weight loss greater than 5% or weight loss greater than 2% in individuals already showing depletion according to current body mass index or skeletal muscle mass [17]. "CDC guideline for prescribing opioids for chronic pain-United States, 2016", which has the highest AAS (n=2324) of the T100 citation list, was an update of a 2014 systematic review on effectiveness and risks of opioids and a supplemental review on benefits, harms, values, preferences and costs. Chronic pain, the use of feared and avoided opioids, and the risks associated with long-term opioid use in chronic pain have attracted the attention of public. This article has been cited 1461 times with a scite score of 1850, with 5 supporting citation statements and no contrasting statements [15]. The article "Complete biosynthesis of opioids in yeast," in which interestingly yeast was designed starting from sugar to produce selected opioid compounds, published in Science in 2015, had one of the highest AASs (n=623) despite being middle of the T100 citation list [18] (Supplement 1, rank 57).

Scite total scores of the articles are lower than the number of citations. While this may seem like a discrepancy, the explanation is actually very simple. While citation counts are based on Web of Science, Scite has a wider network of data. Scite pulls information from major publishers such as Wiley, Sage, British Medical Journal, as well as some smaller publishers and open access publishers' websites, university repositories and preprint repositories that provide access to open access articles.

We found a significant weak correlation between citation count and AAS in T100 citation list ($p=0.001$, $r=0.328$) but no correlation was found between them in T100 altmetric list ($p=0.11$, $r=0.161$). This result showed us that although citation count and AAS are different concepts, valuable articles in the academy resonate with social media, on the other hand, articles popularized by the public are not of the same importance for the academy. In addition, there was a significant correlation between AAS and contrasting citation statement counts ($p=0.024$, $r=0.025$) in T100 altmetric list. This result made us think that altmetric attention scores may be open to manipulation and these articles may be scientifically controversial, as there are many contrasting statements about them.

In a study in which a bibliometric analysis of 217 articles on cancer palliative care was performed, The United States and UK were the countries with the largest number of articles (n=101, n=18, respectively) and this was attributed to the long-term practice of palliative care in these countries. Similarly, the countries with the highest number of articles in our study were the USA, England and Canada (n=53, n=22, n=22, respectively) [19].

It was observed that at least one article was published almost every year between 1992 and 2017 in the T100 citation list, whereas the articles in the T100 altmetric list focused on 2013 and later. This can be attributed to the fact that the place occupied by social media in our lives has increased over the years. The fact that the distribution of the articles in top 100 citation list by year is different from the top 100 altmetric list, and the fact that there

are no articles after 2017 in the T100 citation list, once again shows that the concepts of AAS and citation, and the interest of the academy and the society are different from each other. The publication year of the articles in both the T100 citation and T100 altmetric lists focused on the 2000s. The number of articles published between 2000-2017 in the T100 citation list (n=91) is 9 times the number of articles published between 1975-1999 (n=9). While there was only 1 article published between 1975-1999 in the T100 altmetric list, there were 99 articles published between 2000-2021.This has clearly shown us that the interest in palliative care has increased in the 2000s. The fact that the WHO expanded and renewed the definition of palliative care in 2002 may have been effective in this [20]. In addition, the increasing interest and need for palliative care over the years can be shown as another reason.

Since the approach of palliative care is focused both on the patient and their family, caregivers are also curious about palliative care. For this reason, there are many articles on both the T100 bibliometric (n=10) and the T100 altmetric list (n=11) about caregivers and healthcare professionals interested in palliative care. While there were 6 articles on Covid-19 in T100 altmetric list, no articles were found in the T100 citation list. The Covid 19 pandemic has given all individuals, from academics to the public, a period of restrictions. It has become extremely difficult for patients to access health services and establish contact with healthcare professionals. This situation has tied the hands of terminally ill patients who are at heightened risk from COVID-19 and their caregivers. Patients and caregivers, who did not know what to do and could not reach health professionals, frequently used social media in this period to reach and disseminate information about palliative care. The article "Palliative care for patients with severe covid-19", describes the management of symptoms such as breathlessness, agitation, and anxiety in patients with severe Covid-19, communication with patients and families, and preparing an urgent care plan in case of deterioration and death attracted much attention of society and ranked 4th in the T100 altmetric list with 696 AAS [21]. During the pandemic, the academic community focused more on the etiopathogenesis, prevention and treatment of Covid-19, while WHO provided guidance on how to maintain essential health services, but did not mention palliative care. Based on these, unfortunately, we can say that palliative care services are somewhat neglected during the pandemic by academia [22]. The fact that there are no articles on this subject in the T100 citation list also supports this.

Limitations

Since the citation counts of the articles in the T100 lists were scanned from WoS database, articles not available in this database were not analyzed. The second limitation is that since we searched for the term 'palliative care', articles written as 'end-of-life care' were not included in the study, although it concerns palliative care.

CONCLUSIONS

The article "Early palliative care in patients with metastatic non-small cell lung cancer", written by Temel JS and published in the New England Journal of Medicine, was the article that attracted the most attention of both the academic community and the public in the field of palliative care. Journal of Clinical Oncology was the journal with the highest number of articles in the T100 citation list. Our study revealed the overview of the academy and society on palliative care with a bibliometric and altmetric approach. We showed that the articles that attract the attention of the scientific world also arouse repercussions in social media, while the articles that society is interested in do not arouse much curiosity in the academic community. Although AAS is open to manipulation, it would be beneficial to use altmetric analysis together with bibliometric analysis, as it gives an idea about the topics that the society is curious about. The combined use of bibliometric analysis and altmetric analysis will provide benefits to raise awareness in the society about palliative care and to create new policies.

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Ethical Statement: This study does not require ethics committee approval as data (existing published articles) was collected from a public network platform and analyzed, and did not include human subjects.

Author Contributions: Conception: BBK- Design: BBK- Supervision: BBK- Materials: BBK- Data collection and processing: BBK- Analysis: BBK- Literature: BBK- Review: BBK- Writing: BBK.

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Original Research

Morphological and Morphometric Analysis of the Renal Artery Using Computed Tomographic Angiography

Rabia Taşdemir[1], Cansu Öztürk[1], Rukiye Çiftçi[1], Ömer Faruk Cihan[2]

[1] Department of Anatomy, Faculty of Medicine, Gaziantep Islam Science and Technology University, Gaziantep, Turkey
[2] Department of Anatomy, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey

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Correspondence
Rabia Taşdemir, Phd, Assist. Prof.
Address: Department of Anatomy, Faculty of Medicine, Gaziantep Islam Science and Technology University, Gaziantep, Turkey
E-mail: rabiatsdmr@gmail.com

ABSTRACT

Objective: The anatomical features of the renal arteries are important for the diagnosis of various diseases affecting the kidneys and the renal arteries (RA), as well as for preoperative planning of surgical interventions. The objective of this study was to conduct a comprehensive analysis of the morphological and morphometric parameters of renal arteries specific to the Turkish population.

Methods: RA diameter, angle, and distance to other vessels were performed on computed tomography angiography images of 299 patients (156 women, 143 men), considering their branching variations and the level of origin from the abdominal aorta.

Results: The frequency of RA variations was 16.5%. The right RA was observed to arise between the lower T12 level and middle L4 level, most commonly (25.39%) at the L1-2 disc level. The left RA was found to originate between the upper T12 level and lower L3 level, mostly (27.44%) at the L1-2 disc level. The mean diameter of the right RA was 5.49±1.24 mm in females and 6.01±1.69 mm in males, while the mean diameter of the left RA was 5.96±1.44 mm in females and 6.45±1.74 mm in males. The mean exit angle of the right RA from the abdominal aorta was 57.06±17.27° in females and 57.65±16.62° in males, and that of the left RA was 67.05±18.13° in females and 70.37±17.42° in males. The distance of the right RA to the celiac trunk was 3.1±1.29 cm, and its distance to the aortic bifurcation was 9.56±1.52 cm. The distance of the left RA to the celiac trunk was 3.27±1.25 cm, and its distance to the aortic bifurcation was 9.38±1.41 cm. Analysis of the relationship of the study parameters with age showed statistically significant correlations between age and the left RA diameter and between age and the distance of both the right and left renal arteries to the celiac trunk.

Conclusion: This study could contribute to the literature on renal artery morphology and morphometry in the Turkish population and provide guide clinicians.

Keywords: Angle, Computed tomography angiography, Diameter, Renal artery, Variation

INTRODUCTION

Knowledge of the morphological and morphometric characteristics of the renal arteries (RAs) is of paramount importance in the planning and execution of both open surgical and endovascular interventions on the kidneys and their vasculature [1]. Numerous studies have focused on the anatomical structure of the RA, primarily examining its variations [2-7]. In contrast to the classic anatomy knowledge

that depicts RAs as singular structures on the left and right sides, variations are observed with an incidence ranging from 7.8% to 39% [8, 9]. Variations are explained as the failure of successful regression of several renal arteries that are present during the embryological period [10].

Renal artery variations have been investigated in diverse populations. However, comprehensive studies involving morphometric analyses are limited in number [11-13]. The branching angle of the RA from the abdominal aorta affects the hemodynamics of the blood supply to the kidney [12]. Furthermore, there are studies demonstrating that the diameter of the renal artery affects on the glomerular filtration rate [13].

For physicians performing open surgical or endovascular treatments on the renal artery or the kidney, minimizing complications and achieving a successful operation requires knowledge not only of renal artery variations but also of its exit point from the abdominal aorta, diameter, angle, and distance to other branches originating from the abdominal aorta. The objective of this study was to conduct a comprehensive analysis of the morphological and morphometric parameters of renal arteries specific to the Turkish population.

MATERIALS AND METHODS

Patient Population

This study was conducted retrospectively on archived images of patients who underwent Abdominal Computed Tomography Angiography (CTA) for various reasons at Gaziantep University Faculty of Medicine Hospital between 2015 and 2023. Approximately 2000 patient images identified through archive screening were examined. Images with a slice thickness >5 mm in which the structures were not visible in three-dimensional reconstruction, images affected by motion artifacts, or images with insufficient distribution of contrast material within the artery, compromising image assessment, were excluded. Images from patients who underwent any surgical and/or interventional procedures, those with known kidney disease, and images where the RA and neighboring vessels were not present in the field of view were also excluded from the study. There were no age- or sex-related restrictions for participation in the study. Ultimately, a total of 299 patients meeting the criteria were included in the study. Among them, 156 were female, and 143 were male. The mean age of the patients was 49.85 ± 18.74 years.

Main Points;

- The rate of branching variation of the renal artery was found to be lower than most of the studies in the literature.
- Before the open or endovascular surgical intervention to this area, the origin level, diameter, angle and distance of the renal arteries should be evaluated.

Image Processing

To prepare for the study measurements, two-dimensional CTA images were reconstructed into three-dimensional (3D) images using the open-source software program Horos v.4.0.0 (https://horosproject.org/). Measurements were performed on the coronal plane for angles and on the transverse plane for diameters using the 2D images. Additionally, RA exit levels were determined and distances were measured on the 3D images. Simultaneously, renal artery variations were also noted.

Determination of the vertebral level and morphometric measurements of the renal arteries

The exit point of the renal arteries from the abdominal aorta, and the corresponding point on the vertebral column were identified. To establish the level of the vertebra, four planes were defined that included the lumbar vertebra and intervertebral disc structures: upper (above the pedicle level of the vertebra), middle (at the pedicle level of the vertebra), lower (below the pedicle level of the vertebra), and disc level (intervertebral disc level) (Fig. 1,2). Based on these levels, the levels of the right and left renal arteries (RRA-LRA) and any accessory renal arteries were established separately.

In addition, the exit angles of the renal arteries, their anteroposterior diameters immediately after leaving the abdominal aorta, and distances from the celiac trunk (CT) above and the aortic bifurcation (AB) below were measured. All these measurements were performed separately for the right and left renal arteries, as well as any accessory arteries, if present (Fig. 3).

Statistical Analysis

The descriptive statistics of the study data were presented using mean and standard deviation for numerical variables, and frequency and percentage for categorical variables. Normality of the distribution of renal artery measurements was assessed using

the Shapiro-Wilk test. The independent samples t-test or Mann-Whitney U test was used to compare the categorical variables between two groups as appropriate. The differences between the data for categorical variables were analyzed using the chi-square test. Additionally, relationships between the numerical variables were analyzed using Pearson correlation analysis or Spearman correlation analysis. All statistical analyses were conducted using the SPSS 22.0 (IBM Corp., Armonk, NY), and the significance level was set at $p < 0.05$.

RESULTS

This study was conducted on images from 299 individuals (female, n=156, male, n=143). The age range of the patients was 5-89 years, with a mean age of 49.85±18.74 years. Consistent with classic anatomy knowledge, a single right RA and a single left RA were found in 83.5% of the patients. The frequency of RA variations was 16.5%. Images of the renal artery variations are presented in Fig. 4, and the frequency and percentage of their occurrence in Table 1.

Table 1. Prevalence of variations of the right and left renal arteries.

Number of Right-Left RAs	Number (n=291)	Percentage (%)
1-1	243	83.5
1-2	18	6.3
1-3	1	0.3
2-1	16	5.5
2-2	10	3.4
3-1	3	1.0

RAs: renal arteries

When evaluating the origin of the renal arteries according to the vertebral levels, the right RA was found to arise most commonly at the L1-2 disc level (n=81, 25.39%). This was followed by L1 lower 69 (21.63%), L1 middle 59 (18.5%), L2 upper 47 (14.73%), L1 upper 23 (7.21%), L2 middle 6 (1.88%), T12-L1 disc 5 (1.57%), T12, L3 upper, L3-L4 disc 2 (0.63%). L2-L3 disc, L3 lower, L4 middle level were seen in at least 1 individual (0.31%) each. On the left side, the RA originated mostly from the L1-2 disc level (n=87, 27.44%). This level was followed by L1 lower (56 individuals, 17.67%), L1 middle (51 individuals, 16.9%), L2 upper (43 individuals, 13.56%), L2 middle (24 individuals, 7.57%), L1 upper (22 individuals, 6.94%), T12-L1 disc and L2 lower (11 individuals, 3.47%), L2-L3 disc and L3 upper (4 individuals, 1.26%). 94%), T12-L1 disc and L2 lower (11 individuals, 3.47% each), L2-L3 disc and L3 upper (4 individuals, 1.26% each), T12 upper, T12 lower, L3 middle, L3 lower (1 individual, 0.32% each).

For LRA (left renal artery), Considering the findings from the RA diameter measurements, the mean diameter was 5.6±1.57 mm for the RRA and 6.06±1.64 mm for the LRA. When the RA diameters were analyzed according to sex, statistically significant differences were found in both the right and left renal arteries. The RA diameters were higher in male patients than in females (p=0.001) (Table 2).

For the angular values of the renal arteries, measurements could be performed on 308 arteries for RRA, showing an average angle of 58.04° ± 17.18°. For LRA, angle measurements were obtained from 323 arteries, with a mean angle of 68.51° ± 17.69°. When angular values were evaluated according to sex, no statistically significant difference was observed (p=0.112) (Table 2).

Analyses of the distances of the RA origin to the celiac trunk (CT) above and the aortic bifurcation (AB) below were conducted separately for the right and left renal arteries. The distance between the origin of RRA and CT could be measured in 321 arteries, showing an average distance of 3.1 ± 1.29 cm (p=0.040). The distance between the RRA origin and AB was measured in 320 arteries, with a mean value of 9.56 ± 1.52 cm (p=0.001). In LRA, the mean distance to CT measured in 325 arteries was 3.27 ± 1.25 cm (p=0.168), and the mean distance to AB measured in 324 arteries was 9.38 ± 1.41 cm (p=0.001). Comparing the measured distances between sexes showed a statistically significant difference for all distances, except for the distance between LRA and CT. In all measured distances, the mean distance was greater in males than in females (Table 2).

Lastly, correlations of RA diameter, angle, and distance measurements among each other and with age were analyzed. Only the LRA diameter, RRA-CT distance and LRA-CT distance showed statistically significant correlations with age. A very high positive correlation was observed between LRA-AB distance and RRA-AB distance (p=0.001, r=0.832), as well as a high positive correlation between LRA-CT distance and RRA-CT distance (p=0.001, r=0.712) (Table 3). Due to the limited number of patients in some age groups, the differences in parameters could not be analyzed according to age groups.

Table 2. Distribution of the right and left renal artery diameters, angular values, distance from the origin of the right and left renal arteries to the celiac trunk and aortic bifurcation by sex

	Female		Male		Total		p
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
RRA diameter (mm)	5.49±1.24	5.53 (4.8 -6.29)	6.01±1.69	6.21 (4.97 -7.26)	5.6 ±1.57	(1.08-9.77)	0.001*§
LRA diameter (mm)	5.96±1.44	6.07 (5.11 -6.92)	6.45±1.74	6.67 (5.37 -7.69)	6.06 ±1.64	(0.91-9.91)	0.002*§
RRA angle (°)	57.06±17.27	53.93 (42.89-70.01)	57.65±16.62	56.54 (46-7.78)	58.04±17.18	(12.24-04.43)	0.769‡
LRA angle (°)	67.05±18.13	68.23 (56.77-6.89)	70.37±17.42	70.37 (58.26-1.96)	68.51±17.69	(15.27-22.08)	0.112‡
RRA-CT distance (cm)	2.79±0.78	2.74 (2.21-3.33)	3.03±1	2.99 (2.39-3.55)	3.1±1.29	(0.93-10.36)	0.040*§
LRA- CT distance (cm)	3.03±0.85	3.06 (2.48-3.55)	3.17±0.95	3.2 (2.5-3.83)	3.27±1.25	(0.76-10.83)	0.168‡
RRA-AB distance (cm)	9.45±1.13	9.55 (8.74-10.29)	9.99±1.28	10.04 (9.22-10.88)	9.56±1.52	(1.71-13.45)	0.001*§
LRA-AB distance (cm)	9.18±1.15	9.2 (8.44-10.1)	9.86±1.32	9.85 (9.03-10.76)	9.38±1.41	(3.91-13.37)	0.001*‡

***** Significant difference (p<0.05); **§:** Mann-Whitney U test; ‡: Student's t-test; **RRA:** Right renal artery; **LRA:** Left renal artery; **CT:** celiac trunk; **AB:** aortic bifurcation; **SD:** standard deviation; **Min:** minimum; **Max:** maximum

Table 3. Correlations of the measured parameters with age and among themselves

		Age	RRA diameter	LRA diameter	RRA angle	LRA angle	RRA-CT distance	LRA-CT distance	RRA- AB distance
RRA diameter	r	0.083							
	p	0.153							
LRA diameter	r	**00.444**	**0.605****						
	p	**00.001***	**0.001**						
RRA angle	r	00.111	**-0.130***	**-0.137***					
	p	00.060	**0.023**	**0.020**					
LRA angle	r	00.087	-0.084	-0.099	**0.259****				
	p	00.136	0.144	0.079	**0.001**				
RRA-CT distance	r	**00.478**	-0.055	0.066	**0.158****	-0.031			
	p	**00.001***	0.332	0.252	**0.006**	0.596			
LRA-CT distance	r	**00.277**	0.071	0.091	0.145*	0.088	**0.712****		
	p	**00.001***	0.219	0.105	0.014	0.117	**0.001**		
RRA-AB distance	r	00.045	**0.163****	**0.209****	-0.053	0.094	**-0.452****		
	p	00.448	**0.004**	**0.001**	0.361	0.107	**0.001**		
LRA-AB distance	r	-00.065	0.085	**0.150****	-0.013	-0.001	0.029		
	p	00.268	0.138	**0.007**	0.830	0.979	0.612		

*Significant difference (p<0.05); Pearson and Spearman correlation analyses; RRA: Right renal artery; LRA: Left renal artery; CT: celiac trunk; AB: aortic bifurcation; r: correlation coefficient

Table 4. Correlations of the measured parameters with age and among themselves

		Age	RRA diameter	LRA diameter	RRA angle	LRA angle	RRA-CT distance	LRA-CT distance	RRA- AB distance
RRA diameter	r	.083							
	p	.153							
LRA diameter	r	**0.444**	**.605****						
	p	**0.001***	**.001**						
RRA angle	r	0.111	**-.130***	**-.137***					
	p	0.060	**.023**	**.020**					
LRA angle	r	0.087	-.084	-.099	**.259****				
	p	0.136	.144	.079	**.001**				
RRA-CT distance	r	**0.478**	-.055	.066	**.158****	-.031			
	p	**0.001***	.332	.252	**.006**	.596			
LRA-CT distance	r	**0.277**	.071	.091	.145*	.088	**.712****		
	p	**0.001***	.219	.105	.014	.117	**.001**		
RRA-AB distance	r	0.045	**.163****	**.209****	-.053	.094	**-.452****	-.016	
	p	0.448	**.004**	**.001**	.361	.107	**.001**	.778	
LRA-AB distance	r	-0.065	.085	**.150****	-.013	-.001	.029	**-.352****	**.832****
	p	0.268	.138	**.007**	.830	.979	.612	**.001**	**.001**

***Significant difference (p<0.05); Pearson and Spearman correlation analyses; **RRA:** Right renal artery; **LRA:** Left renal artery; **CT:** celiac trunk; **AB:** aortic bifurcation; r: correlation coefficient

DISCUSSION

In this study, which aimed to make a comprehensive analysis of the morphological and morphometric parameters of the renal arteries specific to the Turkish population, the frequency of RA variations was 16.5%. The right RA was observed to arise between the lower T12 level and middle L4 level, most commonly (25.39%) at the L1-2 disc level. The left RA was found to originate between the upper T12 level and lower L3 level, mostly (27.44%) at the L1-2 disc level. The mean diameter of the right and left RA was narrower in women than in men. While the mean exit angle of the RRA from the abdominal aorta was close in women and men, the LRA was narrower in women than in men.

Since variations of the renal arteries are clinically important, there are numerous studies conducted both on cadavers and using imaging techniques [1, 3, 5-8, 14, 15]. CTA has been reported as a reliable method for studying the arteries, and therefore, measurements of the origin levels, diameters, angles of RA, and distances to other blood vessels have been performed on patients undergoing CTA imaging for various reasons [11].

Variations of Renal Artery

In a retrospective study of renal artery variations in 610 patients, Mihaylova et al. [10] reported that they found a single renal artery on both sides in 46.3% (n=260) and a wide of renal artery variations in 53.7% (n=301). In a postmortem study, Garcia-Barrios et al. [4] observed arterial variations in 75% of 8 cadavers, while Bouzouita et al. [2] reported arterial variations in 9.85% of 71 cadavers. In studies on kidney donors, Aremu et al. [3] reported that 32% of the observed renal artery variations (50%) were multiple renal arteries, while O'Neill et al. [16] found multiple renal artery variations in 45.6% of the patients. Considering RA variations in different populations, the

presence of at least one accessory renal artery was reported at a frequency of 36.1% in the Caribbean population by Johnson et al. [15], with variations of renal artery branching reported in 11.2% of the Greek population by Natsis et al. [14], 38.31% of the Polish population by Sośnik and Sośnik [8], 22% of the Australian population by Tardo et al. [6], and 53.7% of the Bulgarian population by Mihaylova et al. [10]. In the current study, the prevalence of RA branching variations was 16.5%, which is comparable to the results observed in the Greek and Australian populations.

Vertebral Levels of The Origin of The Renal Arteries

Among the published studies investigating the origin levels of the renal arteries, which are crucial for surgical interventions, Fataftah et al. [5] found that both right and left renal arteries originated between the T12-L1 and L2-L3 intervertebral disc levels, most commonly at the L1 vertebral level at a frequency of 41% on both sides. Lee et al. [17] reported that the right renal artery emerged between the T12-L1 intervertebral disc level and the upper margin of L2 vertebra, most commonly at the L1-L2 intervertebral disc level (52%). Mihaylova et al. [10] reported that the renal arteries arose between the T12 and L5 vertebrae, most frequently between the L1-L2 intervertebral disc and the L2 vertebral level. In a study comparing normal renal artery anatomy between sexes, renal arteries were observed to originate between the middle part of the T12 vertebral corpus and the lower part of the L2 vertebra in males, while they emerged between the lower part of the T12 vertebra and the L2-L3 intervertebral disc level in females. In that study, the most common RA origin level in both sexes was found to be between the L1-L2 intervertebral disc [18]. In a study examining the renal artery morphology of 820 patients using computed tomography scans, the authors reported that these arteries, including accessory renal arteries, emerged between the T12 vertebral level and the L3-L4 intervertebral disc level, most commonly at the L1 vertebral level [19]. There are also studies reporting that renal arteries, especially the right renal artery, originate from the thoracic aorta (T10-T12 vertebral levels), albeit rarely [20, 21]. In the present study, both the right and left renal arteries were observed to emerge between the upper part of the T12 and the lower part of the L4, most frequently at the L1-L2 intervertebral disk level on both sides. The most frequently observed origin level is consistent with the literature.

Renal Artery Diameters

It has been reported that the renal artery diameter can be used as a biomarker for estimating the kidney volume, which is one of the key donor parameters assessed in the case of kidney transplantation [22]. As reported in the literature, a RA diameter exceeding the normal value may be associated with potentially fatal aneurysms; in turn, a RA diameter that is below the normal range may be associated with chronic diseases [13, 23, 24]. Identification of the normal RA diameter will be useful in the diagnosis of kidney diseases or in the preoperative evaluation for kidney surgery.

Majos et al. [11] compared RA diameters among variations in a study of 248 patients. They found a significant difference in RA diameter between sexes, with a mean diameter of 5.90 ± 1.1 mm in females and 6.34 ± 1.3 mm in males. In a study of donors, Kesevan et al. [22] reported that the diameter of the right RA was 4.86 ± 0.91 mm and the diameter of the left RA was 5.14 ± 0.85 mm. A study by Aytaç et al. [9] examined the relationship between the renal artery diameter and accessory renal artery reported a mean diameter of 5.86 ± 1.11 mm in renal arteries with normal anatomical branching and noted a reduction in the diameter of the main renal artery in the presence of an accessory renal artery. In a study involving hypertensive patients, measurements showed a left RA diameter of 5.4 ± 1.2 mm and a right RA diameter of 5.2 ± 1.2 mm. The authors reported that the difference was statistically significant, and also noted that patients with lower glomerular filtration rates had significantly reduced RA diameters [13]. In a study on individuals with or without thoracoabdominal aortic aneurysms, the mean diameter of the right RA was 5.4 ± 1.2 mm and that of the left RA was 5.2 ± 0.9 mm. The study found no significant difference between the two groups [25]. In a study involving individuals without any renovascular disease, it was found that the mean diameter of the right RA was 4.59 ± 0.84 mm in females and 5.06 ± 0.99 mm in males. The corresponding figures for the left RA were 4.66 ± 0.84 mm in females and 5.14 ± 0.93 mm in males. Thus, a statistically significant difference was found between sexes in RA diameter on both sides [18]. In a study evaluating renal artery morphometry, a significantly lower main RA diameter was found in the group with an accessory renal artery, with a mean RA diameter of 0.64 ± 0.12 mm in the group without an accessory renal artery versus 0.60 ± 0.11 mm in the group with an accessory renal artery [26]. In the current study, the mean diameter of RRA was 5.6 ± 1.57 mm, and that of LRA was 6.06 ± 1.64 mm, with a significant difference between females and males, which is consistent with literature data.

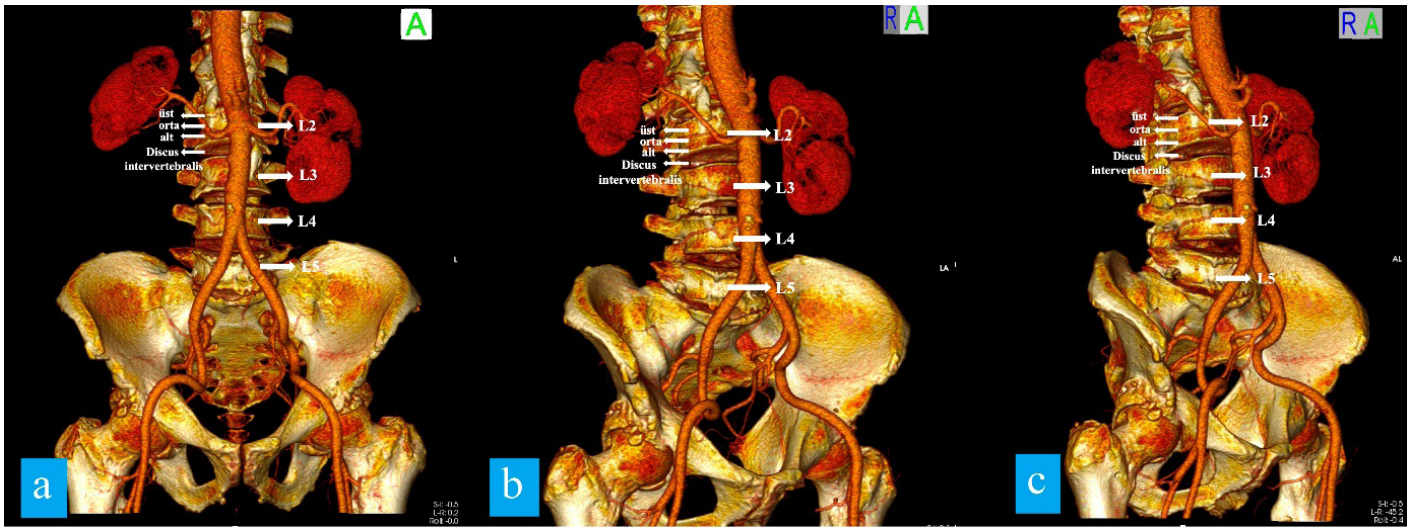

Figure 1. Determination of the origin levels of the right renal arteries concerning the vertebrae. (a) anterior plane, (b) 30° anterolateral plane, (c) 45° anterolateral plane

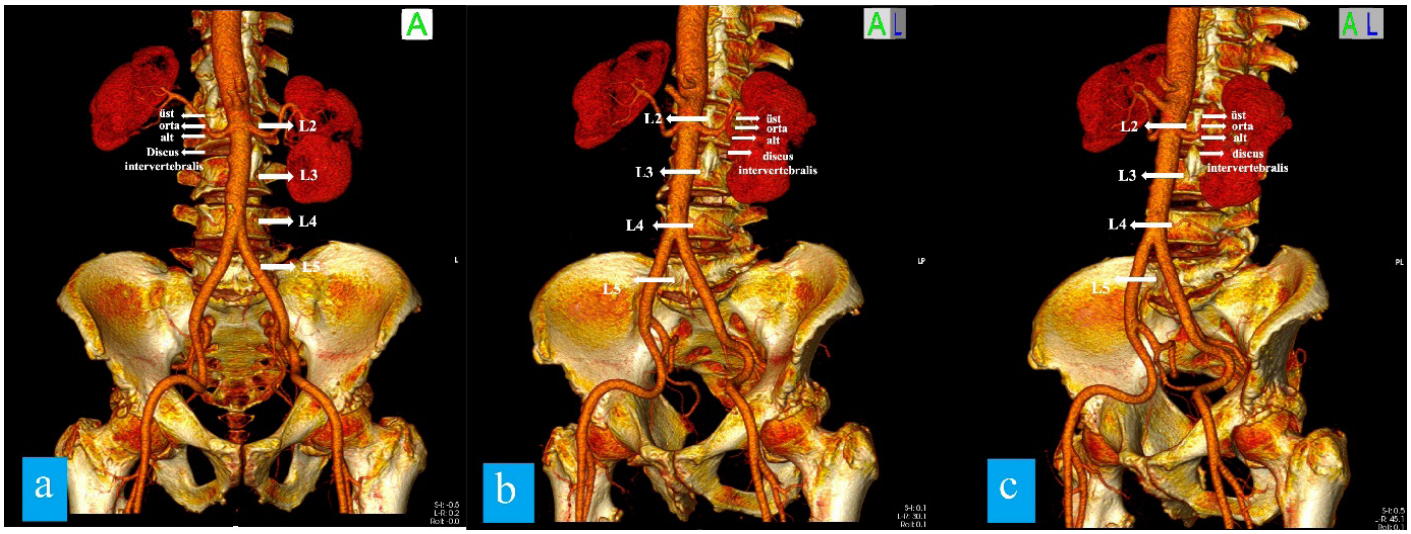

Figure 2. Determination of the origin levels of the left renal arteries concerning the vertebrae. (a) anterior plane, (b) 30° anterolateral plane, (c) 45° anterolateral plane

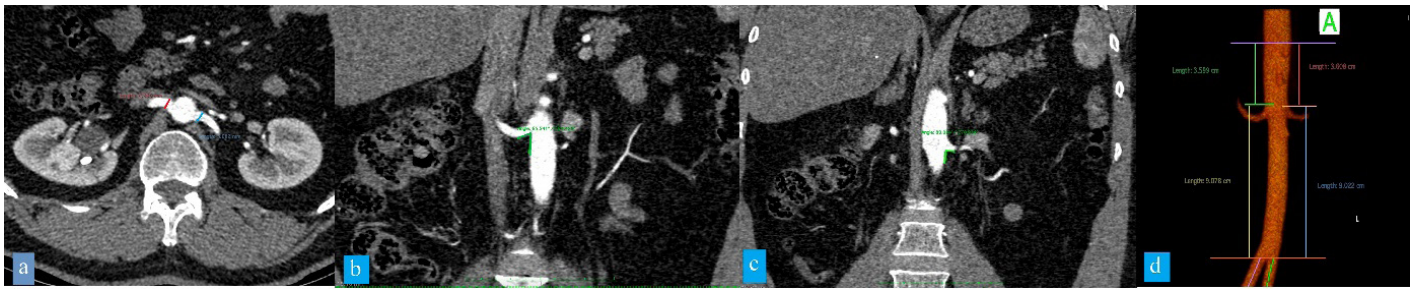

Figure 3. (a) Measurement of diameters of the right (blue line) and left (red line) renal arteries in the transverse plane, (b) Measurement of the take-off angle of the right renal artery from the abdominal aorta (green line) in the coronal plane, (c) Measurement of the take-off angle of the left renal artery from the abdominal aorta (green line) in the coronal plane, (d) Measurement of the distances from the origins of the right and left renal arteries to the celiac trunk and aortic bifurcation in the coronal plane on 3D image.

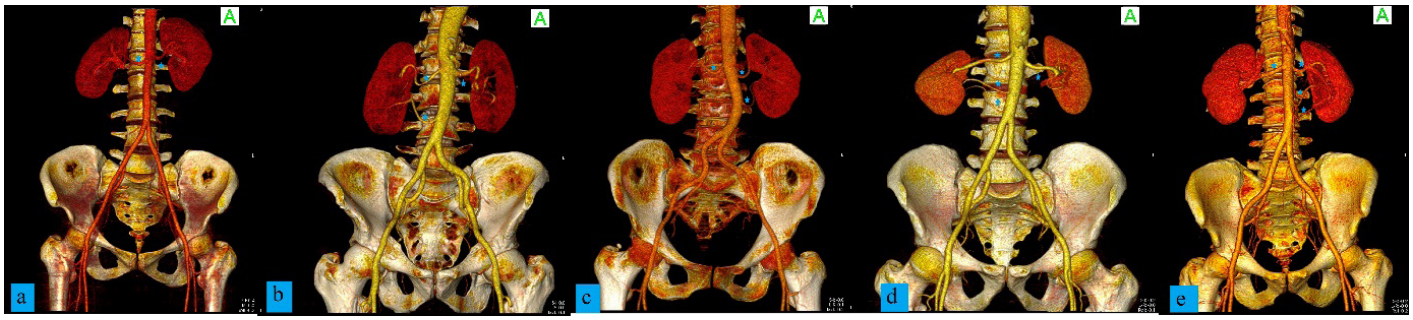

Figure 4. Images of renal artery variations. (a) one right RA and one left RA, (b) two right RAs and one left RA, (c) two left RAs and one RA, (d) two right RAs and two left RAs, (e) three right RAs and one left RA, (f) three left RAs and one right RA.
*: represents the renal arteries.

Renal Artery Angulation

The anatomical angulation formed by the renal arteries when they take off from the aorta is important for the optimal blood supply to the kidney as well as plaque formation and hemodynamics [12, 27]. In the literature, measurements of renal artery angulation have been taken in three different planes including coronal, transverse, and sagittal [12, 18, 25, 27, 28]. Since measurements were obtained in the coronal plane in the current study, a direct comparison with studies measuring in transverse and sagittal planes cannot be made. Csonka et al. [12] reported that the angulation between the renal arteries and the aorta should be between 58° and 78° to maintain constant volume flow and velocity and to avoid changes in turbulence, emphasizing that surgeons should maintain this range of angulation during kidney transplantation to preserve hemodynamic flow. In a study comparing individuals with or without renal artery plaques, Yang and Yang [27] reported that the mean angulation of the right RA was 54.53° ± 17.07° in the group without plaques versus 60.14° ± 14.70° in the group with plaques. For the left renal artery, the group without plaques had a mean angulation of 53.98° ± 15.59° versus 62.79° ± 15.19° in the group with plaques. As such, they reported a significant difference in the renal artery angulation between the control group and the patient group on both sides. In the current study, the mean angulation values were 58.04° ± 17.18° for RRA and 68.51° ± 17.69° for LRA. While these values fall within the limits of normal flow hemodynamics as noted by Csonka et al., they contradict with the findings of Yang & Yang's study. This discrepancy might be explained by the inclusion of individuals without any renovascular disease as well as accessory renal arteries in this study.

Distances of Renal Arteries to CT and AB

Successful endovascular repair (EVAR) requires a thorough understanding of the morphology of the abdominal aorta and its branches [25, 29-31]. Mazzaccaro et al. [25] reported that the distance between RRA and AB was 101.6 ± 19.2 mm, and the distance between LRA and AB was 98.7 ± 20.1 mm. They showed that these distances were significantly longer in the groups with aneurysms compared to healthy individuals. A study investigating infrarenal aortic morphometry in older individuals reported a distance of 90.44 ± 9.82 mm between the lowest renal artery and AB [32]. In a study comparing patients of Asian or Caucasian origin with abdominal aortic aneurysms, the mean RA-AB distance was 143.6 mm in Asians and 116.0 mm in Caucasians [30]. Another study conducting morphometric measurements in individuals with abdominal aortic aneurysms reported a range of 93–210 mm for the distance from the lowest RA to AB [29]. In a study involving individuals with abdominal aortic aneurysms in the Asian population, the distance between the lowest level of the RA and AB was 116.9 ± 13.0 mm [31]. In addition, an anatomical study on cadavers reported that the mean distance between the left RA and CT was 31.9 ± 8.4 mm [33].

In a study on 204 computed tomography images, Arazińska et al. [34] reported a mean RA-CT distance of 25.53±6.59 mm. On the other hand, measurements performed in males aged 18 to 45 years showed that the distance between RA and CT was 16-129 mm (mean, 33 mm) and the distance between RA and AB was 66-123 mm (mean, 97 mm) [35]. These data demonstrate the diversity and variability of renal artery morphometry in different populations and age groups.

In this study, the distances of the right and left renal arteries to the CT were measured separately. The mean RRA-CT distance was 3.1 ± 1.29 cm, RRA-AB distance was 9.56 ± 1.52 cm, LRA-CT distance was 3.27 ± 1.25 cm, and LRA-AB distance was 9.38 ± 1.41 cm, all of which are in line with literature data.

Limitations

It was performed on individuals who applied to the hospital with any complaint but did not have any pathology in terms of renovascular structures and kidneys.

Since this study was designed as a retrospective, demographic information and the presence of another disease that could affect the morphometry of the renal arteries could not be obtained.

CONCLUSIONS

In this study, variations of renal arteries were examined based on their vertebral levels, and their diameters, take-off angles, and distances to CT and AB were measured, contributing to the literature on renal artery morphology and morphometry. The anatomical insights gained through this study can guide preoperative assessments in kidney transplantation, and endovascular or open surgical procedures, potentially leading to interventions with fewer complications and successful outcomes.

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Original Research

Predictors of Mortality in Pulmonary Embolism: A Real-Life Study

Füsun Fakılı[1], Mahşuk Taylan[1], İrem Zehra Bilgiç[1], İrfan Veysel Düzen[2]

[1] Department of Pulmonary Medicine, Gaziantep University Faculty of Medicine, Gaziantep, Turkey
[2] Department of Cardiology, Gaziantep University Faculty of Medicine, Gaziantep, Turkey

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Correspondence
Füsun Fakılı
Address: Department of Pulmonary Medicine, Sahinbey Research Hospital, 1st floor, Gaziantep University, University Boulevard, 27310, Gaziantep, Turkey
E-mail: fusunfakili@yahoo.com
fusunfakili@gantep.edu.tr

ABSTRACT

Objective: The primary aim of this study was to investigate the mortality and associated factors in patients with pulmonary embolism.

Methods: A retrospective analysis was performed on adult patients with pulmonary embolism who applied to Gaziantep University Hospital between January 1, 2017, and January 1, 2023. All-cause mortality and related factors in pulmonary embolism patients were determined.

Results: This study included 152 patients with a median age of 59 years and 81 (53.3%) women. The all-cause mortality rate was 25.7%, and pulmonary embolism-related deaths were 1.3%. Age ($p<0.001$), chronic obstructive pulmonary disease (COPD) ($p=0.013$), heart failure ($p=0.018$), atrial fibrillation ($p=0.015$), massive pulmonary embolism ($p=0.029$), hemoglobin level ($p<0.001$) and NT-Pro BNP level ($p<0.001$) were significantly associated with increased all-cause mortality. In binary logistic regression analysis, for each unit of increasing pulmonary embolism severity index (PESI) score, mortality increased 2.2-fold (95% CI:1.03-5.09), massive PTE 1.6-fold (95% CI:0.14-17.86), anticoagulant duration (daily) 0.98-fold (95% CI:0.98-0.99) and Hb level (per unit Hb reduction) 0.67-fold (95% CI:0.45-1.02) mortality was increasing. There was no statistical difference between the number of hospitalization days for patients with low and high PESI and simplified PE severity index (sPESI) scores.

Conclusions: All-cause mortality in patients with pulmonary embolism increased with age, cardiac diseases, and COPD comorbidities. The PESI and sPESI scores used in the acute phase of PTE were found to be highly reliable in predicting all-cause mortality in PE patients. The diagnosis of massive PE and elevated NT-proBNP levels, a marker of right ventricular dysfunction, were factors that increased mortality.

Keywords: Pulmonary Embolism; Mortality; Risk Factors; Prognosis.

INTRODUCTION

Pulmonary thromboembolism (PTE) is still one of the most common pulmonary vascular diseases with high mortality. The average annual incidence of venous thromboembolism (VTE) is between 23-269/100.000 [1]. The most reported risk factors that increase susceptibility to VTE are a previous history of VTE, active cancer, major trauma, surgery, hospitalization, long flights, immobility, obesity, contraceptives containing estrogen, and concomitant heart diseases [1,2]. Clinical manifestations of PTE; it is divided into three massive, submassive, and nonmassive. Differentiation of the patient diagnosed with acute pulmonary thromboembolism as high-risk, intermediate-risk, or low-risk in terms of early mortality affects treatment options and prognosis [2,3]. Vital signs with electrocardiogram

(ECG), hemogram, lower extremity venous ultrasonography, echocardiography, d-dimer, cardiac troponin, and N-terminus pro-B-type natriuretic peptide (NT-proBNP) tests are used to determine the diagnosis and severity of pulmonary embolism (PE) [2]. The pulmonary embolism severity index (PESI) is used in the prognostic evaluation of PE which is especially effective in determining the first 30-day mortality [4,5]. Respectively, in the study conducted using PESI scoring, early mortality was reported as 0.7% and 1.2% in the low-risk group (Class I and II), while it was reported as 4.8%, 13.6%, and 25% in the high-risk group (Class III-V) [5]. The simplified pulmonary embolism severity index (sPESI), which includes fewer parameters, also had the same efficacy as the PESI index. A score of 0 indicates a low risk for a 30-day poor prognosis and a score of 1 ≥ indicates a high risk for a poor 30-day prognosis [6].

Although outpatient treatment is recommended for patients with low-risk PE with stable hemodynamics, they are still treated as inpatients for an average of 4 days in early discharge and 9 days in long hospitalizations [7]. It can be fatal at varying rates according to co-morbidities, risk status, and the clinical severity of PE. In a large recording study, the 30-day mortality due to PE was 1.8%, and the seven-day mortality was 1.1%. In the same cohort, all-cause mortality was 4.8% at 30 days and 1.9% at seven days [8]. Randomized controlled trials, prospective cohort treatment studies, and meta-analyses reported no difference in treatment efficacy and safety (recurrence, bleeding, and mortality) in nonmassive PTE patients with low risk of complications when compared to outpatient and inpatient treatment [2,9]. Clinically stable, with good cardiopulmonary reserve, low PESI or SPESI scores, easy access to treatment centers when necessary, and treatment compliance, 13-51% of patients were eligible for early discharge and outpatient treatment [9,10].

Main Points;

- The pulmonary embolism severity index (PESI) and simplified PE severity index (sPESI) used in the acute phase of PTE were quite reliable in predicting all-cause mortality in patients with pulmonary embolism.
- PESI score, massive PTE, Hb level, and NT-Pro BNP level were independent factors in pulmonary embolism-related mortality.
- No statistically significant difference was found in the mean hospitalization days of patients with sPESI scores of 0 and 1.

Although there are studies on in-hospital and first-trimester mortality rates of patients with pulmonary embolism, real-life data on long-term mortality rates are limited [11]. Determining pulmonary embolism severity and mortality determinants will facilitate the follow-up of patients. The primary aim of this study was to investigate the mortality and associated factors of patients with pulmonary embolism who were retrospectively diagnosed and treated in our hospital. The secondary purpose was to compare PESI or sPESI scores with outpatient and inpatient treatment rates and mortality rates for patients.

MATERIALS AND METHODS

Study Design and Participants

The design of this study is an observational, cross-sectional, retrospective study. This study was approved by the Gaziantep University Medical Ethics Committee (No. S-2022-268) and all steps were carried out in accordance with the principles of the Declaration of Helsinki.

This study included outpatient and/or inpatient patients older than 18 years of age who were diagnosed with pulmonary embolism and who were admitted to the department of pulmonary medicine and cardiology of the tertiary care hospital between January 1, 2017 and January 1, 2023. Cases with a definitive diagnosis of pulmonary embolism clinically and radiologically confirmed by spiral computed tomography (CT)-angiography or ventilation-perfusion scintigraphy were included in the study. The presence of deep vein thrombosis (DVT) was considered to be DVT in cases demonstrated by doppler ultrasound. Patients with clinical DVT findings but no findings on doppler ultrasound were considered to have no DVT. For massive PTE, hemodynamic instability parameters [need for cardiopulmonary resuscitation; systolic blood pressure < 90 mmHg; need for vasopressors to maintain systolic blood pressure ≥ 90 mmHg despite adequate fluid support; and presence of concomitant end-organ hypoperfusion (altered consciousness, oliguria/anuria, increased serum lactate level, systolic blood pressure drop of more than 40 mmHg) and/or echocardiographic findings] were required.

Patients with suspected PTE, cases with an unclear diagnosis that resulted in exitus at the time of diagnosis, no radiological evidence of thrombus by spiral CT-angiography or ventilation-perfusion scintigraphy, and chronic thromboembolic pulmonary hypertension (CTEPH) at presentation were all excluded.

Data Collection

Pulse rate, blood pressure, oxygen saturation (%SpO2), body mass index (BMI), comorbidities, previous history of VTE, hemogram, d-dimer, cardiac markers (NT-proBNP, troponin), echocardiography findings, sPESI, PESI score, diagnosis of massive PE, need for intensive care unit (ICU), length of hospital stay, anticoagulant treatments received, and deaths in hospital and after discharge were recorded. Since the study covered the pandemic period, those who were diagnosed with COVID-19 at the time of diagnosis and those whose cause of death was COVID-19 were recorded.

Anticoagulant therapies [low molecular weight heparin (LMWH), warfarin, new oral anti-coagulant (NOAC)], duration, and need for a vena cava filter were recorded at initial diagnosis and on the seventh day/after discharge. All-cause deaths while receiving PE treatment were recorded.

Statistical Analysis

IBM SPSS version 25.0 was used for statistical analysis. The compatibility of the numerical variables with normal distribution was tested by Shapiro-Wilk test. Mean and the standard deviation were used to represent the data fitting the normal distribution, and median values were used for those not fitting the normal distribution. Patients were divided into two subcategories as deceased and living groups according to their survival status The association of categorical variables with mortality calculated by chi-square analysis. The association of normally distributed numerical variables with mortality was measured by Student-T test, and the association of non-normally distributed variables with mortality were measured by Mann-Whitney U test. Binary logistic regression analysis was used to determine the independent factors determining mortality. In statistical analysis, $P<0.05$ was considered statistically significant at 95% confidence interval.

RESULTS

Study Population

The retrospective study included 152 patients with a median age of 59 years and 81 (53.3%) women. BMI (mean±SD) was 32.7±7.8. Concurrent with pulmonary embolism, 38.7% of the patients had DVT. A previous VTE was seen in 9.9% of the patients. The most common comorbidity was hypertension (27%), followed by diabetes mellitus (25%). COVID-19 was found in 13.5% of the patients at the time of PE diagnosis. Systolic blood pressure (SBP) (mean±SD) at admission was 119±19 mmHg, heart rate/min (mean±SD) was 94±16, and median respiratory rate/min was 22. In the echocardiography of the patients, the mean (mean±SD) sPAP was 38±20 mmHg, and 34% had right ventricular dysfunction. The sPESI score of 43.9% of the patients was 1 point. Of the study population, 17.3% were diagnosed with massive pulmonary embolism, and 28.9% needed an intensive care unit (ICU). In the study population, all patients were started on anticoagulant therapy, and one patient had a vena cava filter inserted due to bleeding. The duration of hospitalization (mean±SD) was 11±10 days. The duration of anticoagulant therapy for pulmonary embolism in the cohort was (mean±SD) 269±322 days (Table 1).

Table 1. Descriptive Statistics

Characteristics of the Patients (n=152)	n (%)
Age, years, median (min-max)	59 (17-92)
Female	81 (53.3)
BMI, mean ± SD	32.7±7.8
Family history of PTE	3 (2)
Hypertension	41 (27)
Diabetes mellitus	38 (25)
Chronic kidney disease	5 (3.3)
History of cancer	17 (11.2)
Active cancer	13 (8.6)
COPD	16 (10.5)
Heart failure	16 (10.5)
Atrial fibrillation	2 (1.3)
Connective tissue disease	3 (2)
History of MI	16 (10.6)
History of stroke	10 (6.6)
History of VTE	15 (9.9)
AFS	2 (5.1)
COVID-19 at diagnosis	20 (13.5)
Varicose vein	7 (6.2)
DVT at diagnosis	43 (38.7)
SBP (mmHg), mean±SD	119±19
HR/min, mean±SD	94±16
RR/ min, median (min-max)	22 (15-30)
spO2%, mean±SD	92±7
D-dimer (µg/L), median (min-max)	3.6 (0.23-35.2)
Troponin (ng/mL), median (min-max)	9.1 (0.01-4560.3)
NT-Pro BNP (pg/mL), median (min-max)	840.4 (10-23950)
Hb, median (min-max)	12.9±2
Platelets (10^9/L), mean±SD	280±115
sPAP(mmHg), mean±SD	38±20
Right ventricular dysfunction	35 (34)

PESI	2±1	
sPESI	0	83 (56.1)
	1	65 (43.9)
ICU	44 (28.9)	
Massive PTE	26 (17.3)	
Warfarin	91 (60.3)	
LMWH	147 (97.4)	
NOAC	79 (52.3)	
Unfractionated heparin	10 (6.6)	
Vena cava filter	1 (0.7)	
Hospitalization (days), mean±SD	11±10	
Anticoagulation therapy (days), mean±SD	269±322	
All-cause of deaths	39 (25.7)	
Cardiovascular deaths	10 (6.9)	
PE-related deaths	2 (1.3)	
Bleeding-related deaths	1 (0.7)	
Cancer-related deaths	8 (5.7)	
Non-cardiovascular non-cancer deaths	11 (7.7)	
Unknown deaths	9 (6.1)	
COVID-19-related deaths	2 (1.4)	

SD; Standard deviation, **BMI;** Body mass index, **PTE;** Pulmonary thromboembolism, **COPD;** Chronic obstructive pulmonary disease, **MI;** Myocardial infarction, **VTE;** Venous thromboembolism, **AFS;** Antiphospholipid syndrome, **DVT;** Deep vein thrombosis, **SBP;** Systolic blood pressure, **HR;** Heart rate, **RR;** Respiratory rate, **LMWH;** Low molecular weight heparin, **NOAC;** New oral anti-coagulant.

Mortality and Affecting Factors Analysis

The all-cause mortality rate of the study population was 25.7%. When the causes of mortality were analyzed; cancer and non-cardiovascular deaths were 7.7%, cardiovascular deaths were 6.9%, deaths of unknown cause were 6.1%, cancer-related deaths were 5.7%, COVID-19-related deaths were 1.4%, VTE-related deaths were 1.3%, and bleeding-related deaths were 0.7%. When the factors associated with mortality in pulmonary embolism patients in the survival and mortality groups were univariate analyzed, age ($p<0.001$), chronic obstructive pulmonary disease (COPD) ($p=0.013$), heart failure ($p=0.018$), and atrial fibrillation ($p=0.015$) were significantly associated with increased mortality. The diagnosis of massive PTE was a factor that significantly increased mortality ($p=0.029$). Among the scalar variables, decreased hemoglobin (Hb) level ($p<0.001$) and increased NT-Pro BNP level ($p<0.001$) were associated with increased mortality.

In the retrospective data analysis, all patients with pulmonary embolism received either LMWH or unfractionated heparin at first admission. Taking warfarin ($p=0.05$) or NOAC ($p=0.044$) as anticoagulant therapy was associated with significantly reduced mortality. Prolonged anticoagulant treatment duration (days) was associated with reduced mortality ($p<0.001$) (Table 2).

For factors influencing mortality, a multivariate analysis was undertaken. A binary logistic regression analysis was performed to determine the factors independently affecting mortality in pulmonary embolism; for each unit of increasing PESI score, 2.2-fold (95% CI: 1.03-5.09), massive PTE 1.6-fold (95% CI: 0.14-17.86), anticoagulant duration (per day) 0.98-fold (95% CI: 0.98-0.99), and Hb level (Table 3).

Table 2. Factors related to mortality

		Life status		p value
		Alive	Death	
		n (%)	n (%)	
Gender	Female	55 (67.9)	26 (32.1)	0.052
	Male	58 (81.7)	13 (18.3)	
Family history of PTE	no	110 (74.3)	38 (25.7)	
	yes	2 (66.7)	1 (33.3)	0.764
Hypertension	no	85 (76.6)	26 (23.4)	
	yes	28 (68.3)	13 (31.7)	0.299
Diabetes mellitus	no	87 (76.3)	27 (23.7)	
	yes	26 (68.4)	12 (31.6)	0.335
Chronic kidney disease	no	108 (73.5)	39 (26.5)	
	yes	5 (100)	0 (0)	0.182

History of cancer	no	103 (76.3)	32 (23.7)	
	yes	10 (58.8)	7 (41.2)	0.120
Active cancer at diagnosis	no	105 (76.1)	33 (23.9)	
	yes	7 (53.8)	6 (46.2)	0.080
COPD	no	97 (71.3)	39 (28.7)	
	yes	16 (100)	0 (0)	**0.013***
Heart failure	no	105 (77.2)	31 (22.8)	
	yes	8 (50)	8 (50)	**0.018***
Atrial fibrillation	no	113 (75.3)	37 (24.7)	
	yes	0 (0)	2 (100)	**0.015***
Connective tissue disease	no	110 (73.8)	39 (26.2)	
	yes	3 (100)	0 (0)	0.304
History of MI	no	103 (76.3)	32 (23.7)	
	yes	10 (62.5)	6 (37.5)	0.229
History of stroke	no	106 (74.6)	36 (25.4)	
	yes	7 (70)	3 (30)	0.745
History of VTE	no	101 (74.3)	35 (25.7)	
	yes	12 (80)	3 (20)	0.627
AFS	no	31 (83.8)	6 (16.2)	
	yes	2 (100)	0 (0)	0.536
COVID-19 at diagnosis	no	96 (75)	32 (25)	
	yes	15 (75)	5 (25)	1.000
Varicose Vein	no	85 (80.2)	21 (19.8)	
	yes	7 (100)	0 (0)	0.192
DVT at diagnosis	no	55 (80.9)	13 (19.1)	
	yes	35 (81.4)	8 (18.6)	0.946
Right ventricular dysfunction	no	54 (79.4)	14 (20.6)	
	yes	25 (71.4)	10 (28.6)	0.364
ICU	no	83 (76.9)	25 (23.1)	
	yes	30 (68.2)	14 (31.8)	0.267
Massive PTE	no	97 (78.2)	27 (21.8)	
	yes	15 (57.7)	11 (42.3)	**0.029***
Warfarin	no	37 (61.7)	23 (38.3)	
	yes	75 (82.4)	16 (17.6)	**0.004***
LMWH	no	3 (75)	1 (25)	
	yes	109 (74.1)	38 (25.9)	0.969
NOAC	no	48 (66.7)	24 (33.3)	
	yes	64 (81)	15 (19)	**0.044***
Unfractionated heparin	no	105 (74.5)	36 (25.5)	
	yes	7 (70)	3 (30)	0.755
Vena cava filter	no	112 (74.7)	38 (25.3)	
	yes	0 (0)	1 (100)	0.089

Chi-square Test. *Significant at the 0.05 level. **PTE:** Pulmonary thromboembolism**, COPD:** Chronic obstructive pulmonary disease. **MI:** Myocardial infarction. **VTE:** Venous thromboembolism. **AFS:** Antiphospholipid syndrome. **DVT:** Deep vein thrombosis, **ICU:** intensive care unit **LMWH:** Low molecular weight heparin. **NOAC:** New oral anti-coagulant.

Table 3. Binary Regression Analysis for Determining Factors Predicting Mortality in Pulmonary Embolism

Variables	B	S.E.	Wald	df	Sig.	Exp(B) 95% C.I.
NT-Pro BNP	0.00	0.00	2.28	1	0.131	1.000 (1.0-1.0)
Hb	-0.38	0.20	3.47	1	0.062	0.678 (0.45-1.02)
PESI score	0.83	0.40	4.18	1	0.041	2.298 (1.03-5.09)
Anticoagulation therapy (days)	-0.01	0.005	5.74	1	0.016	0.989 (0.98-0.99)
Atrial fibrillation	-19.89	40192.99	0.00	1	1.000	0.000 (0-0)
Massive PE	0.47	1.23	0.14	1	0.702	1.601 (0.14-17.86)
Constant	22.25	40192.99	0.00	1	1.000	4614585140.462

a.Variables: NT-Pro BNP, Hb (hemoglobin), PESI, Anticoagulation therapy (days), Atrial fibrillation. Massive PE (Pulmonary embolism), NOAC (new oral anti-coagulant). Confidence interval (CI).

Nagelkerke R Square: 0.647

Pulmonary Embolism Risk Scoring Analysis

The mean hospitalization day of patients with sPESI score 0 was 10.6±10.6 and 12.1±8.6 for patients with sPESI score 1, and no statistically significant difference was found between the two groups in terms of hospitalization days (p=0.332). In the analysis of all-cause mortality in the study registry, there was a statistically significant increase in mortality with increasing PESI score (p<0.001) and sPESI ≥ 1 (p<0.001) scores.

DISCUSSION

In this study, real-life mortality rates and associated factors for patients diagnosed with PTE were shown. In the study, the mortality rate due to pulmonary embolism was 1.3% and the all-cause mortality rate was 25.7%. In a retrospective pulmonary embolism study of 1023 patients with a mean follow-up of 4 years, the all-cause mortality rate was 35.5%, which is higher than the present study. In the same study, the most common causes of mortality after discharge were malignancy, cardiovascular and sepsis [12]. In this study, the non-cardiovascular non-cancer death rate, which includes infection and other causes, was the highest, with cardiovascular death ranking second and cancer-related death ranking third. In a long-term mortality study of pulmonary embolism in Turkey, mortality rates were 13.3% (95% CI: 10.1-16.7) at 30 days, 21.8% (95% CI: 17.8-25.9) at 90 days, 32.6% (95% CI: 28.1-37.0) at one year and 51% (95% CI: 46.0-55.8) at five years [13]. Previously, in a large multicenter study involving 123 countries for the investigation of deaths due to pulmonary embolism, it was shown that all deaths due to pulmonary embolism increased with age, although the rates differed according to countries, as in our study [14].

When the factors affecting all-cause mortality are analyzed, comorbidities of lung and heart diseases appear to be the factors that increase mortality. The comorbidities (heart and lung diseases) in the PESI scoring, which are more useful in predicting 30-day mortality, may similarly be useful in predicting long-term mortality [4,5]. In previous retrospective and prospective studies, the presence of cancer was found to be a factor associated with mortality in patients with pulmonary embolism [4,8,12,13,15]. In our study, a history of cancer or active cancer did not make a statistically significant difference in all-cause mortality. Variables included in the PESI scoring were not included in the regression analysis. In regression analysis of this cohort, each unit increase in PESI scoring increased all-cause mortality by 2.2-fold (95% CI: 1.03-5.09). PESI scoring at the PTE diagnosis stage has been useful in predicting mortality in this study. The statistical significance of PESI and sPESI scoring for mortality after 30 days in PTE was also shown in another study [13]. In our study cohort, the association of SBP value, heart rate, respiratory rate, respiratory rate, oxygen saturation percentage, and paO2 vital scalar values at diagnosis with all-cause mortality was not statistically significant. However, tachycardia, low SBP, respiratory failure (tachypnea and/or low SaO2), and syncope, alone or in combination, were associated with an increased risk of short-term pulmonary embolism mortality in acute PTE [2,4]. Although vital signs at diagnosis are important for acute pulmonary embolism mortality, their long-term effect is not clear. Our study found no statistically significant association between right ventricular (RV) dysfunction and sPAP with mortality. A meta-analysis suggested that RV dysfunction on echocardiography is associated with an increased risk of short-term mortality in patients who appear hemodynamically stable on admission [16]. In our study, massive PTE was found to be an independent risk factor for mortality. In previous studies, massive PTE short- and long-term mortality rates were higher than nonmassive PTE [3,17,18]. A large case series study showed a 17.5-fold increased risk of fatal PTE in patients presenting with symptomatic massive PTE [3]. In the regression analysis

performed in this study, patients with a diagnosis of massive PTE had a 1.6-fold (95% CI: 0.14-17.86) increase in all-cause mortality. It was previously shown that thrombolytic therapy in acute massive pulmonary embolism made no difference in long-term mortality after 30 days [19]. Therefore, close follow-up of patients diagnosed with massive PTE who received thrombolytic therapy in the acute phase and who received anticoagulants may be useful after discharge. In this study, blood Hb values and NT-proBNP levels, which were not included in PESI scoring, were associated with all-cause mortality. Plasma levels of natriuretic peptides reflect the severity of right ventricular dysfunction and hemodynamic impairment in acute PTE [20]. Post-discharge cardiac and hemodynamic follow-up of patients with elevated NT-proBNP levels may be useful. The presence of echocardiographic RV dysfunction or elevated natriuretic peptides in pulmonary embolism patients has been associated with short-term mortality without hemodynamic deterioration [16]. In a 183-case study on long-term mortality due to PTE, there was no significant difference between the Hb parameter and pulmonary embolism clinical risk groups [11]. The Hb level was not included in PTE risk scoring in the PESI validation study [4,5]. However, in the 30-day mortality predictor model of the large acute pulmonary embolism study, each unit change in Hb level was statistically significant [8]. Control of blood Hb levels during anticoagulant treatment of pulmonary embolism patients may be critical in those at risk of bleeding. In the regression analysis of the study, a 0.98-fold (95% CI: 0.98-0.99) significant reduction in mortality was found as the duration (days) of anticoagulant therapy was prolonged. All-cause mortality among PTE patients receiving prolonged treatment was also reduced. Similarly, another previous study showed a statistically significant decrease in mortality (p=0.026) in patients receiving heparin therapy on PTE days 31-90 [13].

In this study, no statistically significant difference was found in the mean hospitalization days of patients with sPESI scores of 0 and 1. Early discharge and outpatient treatment are recommended for patients with clinically and cardiopulmonary stable PESI or low sPESI scores [9,10]. However, as seen in our study, pulmonary embolism patients had a similar number of hospitalization days even though the PESI score was low. Physicians preferred to give anticoagulant treatment during hospitalization. Transportation to the hospital, social support, and difficulty in follow-up may have been effective in this decision.

Limitations

This is a single-center, retrospective, observational cohort study with all of the limitations inherent in this type of study. Given the retrospective study design, data were missing for some variables.

CONCLUSIONS

In conclusion, all-cause mortality in patients with pulmonary embolism increased with age, cardiac diseases, and COPD comorbidities. The PESI and sPESI scores used in the acute phase of PTE were found to be highly reliable in predicting all-cause mortality in PE patients. The diagnosis of massive PE and elevated NT-proBNP levels, a marker of right ventricular dysfunction, were factors that increased mortality. Patients with low PESI and sPESI scores were hospitalized as much as patients with high scores, and outpatient follow-up was not preferred.

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Conflict of interest: None to declare.

Ethical Approval: This study was approved by the Gaziantep University Medical Ethics Committee (No: S-2022-368). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Contribution of the Authors: FF and IVD designed the study; FF and IZB collected the data; FF and MT analyzed the data; FF searched the literature and wrote the manuscript; FF edited and revised the manuscript according to the journal's instructions; FF and MT edited and controlled the final version of the manuscript. All the authors approved the final version of the manuscript.

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Original Research

Karolinska Sleepiness Scale is not Associated with Obstructive Sleep Apnea Severity Indices in Male Taxi Drivers

Yeliz Çelik[1]

[1] Koc University Research Center for Translational Medicine (KUTTAM), Koc University, Istanbul, Turkey

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Correspondence
Yeliz Çelik, PhD
Address: Koc University Research Center for Translational Medicine (KUTTAM), Koc University, Istanbul, Turkey
E-mail: yecelik@ku.edu.tr

ABSTRACT

Objective: In the current study, we aimed to evaluate the diagnostic utility of the Karolinska Sleepiness Scale (KSS) for obstructive sleep apnea (OSA) in taxi drivers.

Methods: Forty male professional taxi drivers who participated in a driving simulator experiment in the sleep laboratory were included in the current study. All participants were asked to fill out the KSS before and after a 50-minute driving simulator task in the morning after overnight polysomnography (PSG) in the hospital. OSA was defined as an apnea-hypopnea-index (AHI) 15 events/hour on the PSG. Excessive daytime sleepiness (EDS) was defined as KSS score of at least 6.

Results: In all, only 3 cases fulfilled the criteria for EDS before the driving whereas 13 cases were sleepy after the task was completed (p <0.001). No significant association was found between KSS scores after the task and the PSG variables including total sleep time, time spent in delta sleep and REM sleep as well as OSA severity indices AHI and Oxygen Desaturation Index (ODI). The agreement between OSA and sleepiness on the KSS was calculated as 0.21 (p=0.07) indicating a very weak association. The KSS has a sensitivity of 24.1%, a specificity of 45.5%, a positive predictive value of 53.9%, a negative predictive value of 30.0%, an accuracy of 46.6% for the OSA diagnosis. The area under the curve was 0.57 (95% CI 0.39 – 0.74) for the AHI and 0.56 (95% CI 0.39 – 0.73) for the ODI, confirming a very poor performance of the KSS scores to predict AHI and ODI.

Conclusion: The KSS is not associated with the severity of the OSA indices in male taxi drivers. Objective measurements of EDS are warranted for a more precise evaluation of fitness to drive in professional drivers.

Keywords: Obstructive sleep apnea, daytime sleepiness, sleep testing

INTRODUCTION

Motor vehicle accidents (MVAs) remain one of the most prominent contributors to both fatalities and injuries not only worldwide, but also in Turkey [1, 2]. A recent review reported that 95% of the MVAs result from driver-related factors including high speed, alcohol consumption, substance use, fatigue, and daytime sleepiness [3].

Excessive sleepiness (EDS) is defined as an inability to maintain alertness and wakefulness during the major waking episodes of the day [4]. The occurrence of EDS has been estimated at around 30% in cardiac cohorts [5, 6] and up to 15% in general populations [7]. Turkish Adult Population Epidemiology of Sleep (TAPES) study estimated the ESS prevalence as 5.4% in

Turkey using a questionnaire-based method [8].

A medical disorder causing EDS is obstructive sleep apnea (OSA), which is a sleep breathing disorder characterized by intermittent episodes of upper airway obstruction (complete/partial) during sleep, resulting in intermittent hypoxia, variation in blood pressure sleep fragmentation, and increased activation in the sympathetic nervous system [6]. The OSA prevalence was reported up to 17% in the general population and it is more common in the elderly population [9]. Based on the TAPES study, the OSA prevalence is around 14% in the general population in Turkey [8]. OSA patients with daytime sleepiness have been associated with an increased risk for MVAs [1, 2, 10].

There are several self-rating questionnaires for EDS to use in the general population as well as sleep clinical cohorts. Karolinska Sleepiness Scale (KSS) is a one-dimensional Likert scale measuring the subjective sleepiness level at a particular time [11]. It has been demonstrated that falling asleep at the wheel during the simulator task is preceded by an enhanced score on the KSS [12]. KSS is used for both females and males and it is effective in measuring the changes in response to environmental factors [11]. There is yet no report regarding the association of sleepiness level measured with KSS and OSA severity in a sleep clinic cohort. The current study aims to examine the diagnostic utility of the KSS to predict OSA severity among male taxi drivers.

Main Points;

- The Karolinska Sleepiness Scale is not associated with the severity of obstructive sleep apnea indices in male taxi drivers.
- It can be used for measuring the changes in sleepiness levels of drivers during simulator tasks.
- Notwithstanding, these changes do not correlate with polysomnography variables including total sleep time, time in Delta and REM sleep as well obstructive sleep apnea severity indices apnea-hypopnea-index and oxygen desaturation index.
- The sensitivity, specificity, and accuracy values as well as the positive and negative predictive values suggest a poor performance of the Karolinska Sleepiness Scale to screen for obstructive sleep apnea (24.14%, 45.5%, 46.6%, 53.9%, and 30.0%, respectively).

MATERIALS AND METHODS

Participants

The current research includes 40 male taxi drivers who were recruited from the Sleep Laboratory at Koç University Hospital, Istanbul, for the driving simulator study. The participants were asked to fill out questionnaires and undergo an overnight hospital PSG. Participants were asked to refrain from consuming coffee and energy drinks, in addition to avoiding other stimulants before the overnight attendant hospital sleep testing. The inclusion criteria of the current study were having a driving license for more than three years and having been working as a taxi driver actively at least 6 or 7 days a week. Participants were deemed ineligible in case of having acute illness, and no longer held a valid driver's license. All subjects were invited to voluntarily participate in the present study, and they provided written informed consent. The study protocol has been approved by the Koç University Committee on Human Research (2020.292.IRB2.083; 19 June 2020). Each participant provided written informed consent.

Data Collection and Definition

Baseline demographic characteristics as well we comorbidities were documented. Body mass index (BMI) $\geq 30 kg/m^2$ was used to define obesity. Each participant filled out a questionnaire asking for information on sleep-related symptoms, and sleep habits, which were used in clinical routines. The KSS was administered before and after the driving simulator test to assess sleepiness.

Driving Simulator Test

Participants meeting inclusion criteria were scheduled for a driving session between 08:00 AM and 10:00 AM following the PSG. The lights in the cabin room were turned off and the door was closed. Each participant engaged in a fifty-minute simulated driving session on a two-way highway, with traffic density maintained at a low level. The XBUS PRO Driver Training Simulator (DTS), developed by ANGRUP Co. was used in the current study (Figure 1).

Karolinska Sleepiness Scale

KSS is a self-rated questionnaire assessing the subjective sleepiness level using a Likert scale ranging from 1 (Extremely alert) to 9 (Extremely sleepy, great effort to keep alert, fighting sleep) (Table 1). Although a score of 7 or more was suggested for EDS based on variations in electroencephalogram and electrooculogram recordings [11, 13], a recent study has reported

that KSS exists in two versions, which are like each other with a high agreement and both versions can be used interchangeable [14]. Based on those results, a score of 6 was used as a threshold for sleepiness in the present study (Table 1).

Figure. 1. Driving simulator task.

Table 1. Items of the KSS and the categorization criteria used in the present study.

Version A (Original Scale)	**Version B**	**Categorization**
Item 1 Extremely alert	**Item 2** Very alert	No sleepiness
Item 3 Alert	**Item 4** Rather alert	
Item 5 Neither alert nor sleepy		No sleepiness
Item 7 Sleepy but no effort to keep awake	**Item 6** Some sign of sleepiness	Sleepiness
Item 9 Very sleepy, great effort to keep awake, fighting sleep	**Item 8** Sleepy, but some effort to keep awake	

Sleep Measurement

In the current study, a full-night PSG (NOX-A1 system; Nox Medical Inc., Reykjavik, Iceland) was conducted in the hospital and included EEG, EOG, chin and leg electromyograms, nasal airflow, thoracoabdominal and leg movements, body position, heart rate, and SpO^2. Sleep stages, arousals, apneas and hypopneas were scored based on The AASM 2012 criteria [15]. The oxygen desaturation index (ODI) was calculated as the number of significant desaturations (at least 3% from baseline). OSA was defined as an AHI ≥ 15 events/h of the total sleep time [16].

Statistical Analysis

Descriptive statistics were summarized as median with 25th and 75th percentile for the continuous variables, and as count with percentage for the categorical variables. Shapiro-Wilk Test was used for the normality assumptions. Regarding between-group differences, the Mann–Whitney U Rank Test was used for continuous variables, and χ^2 test or Fisher's Exact Test was used for the categorical variables. For the within-group comparisons, the Wilcoxon Nonparametric Test and the McNemar Nonparametric Test were used to analyze continuous and categorical variables, respectively. The agreement between OSA and KSS classification was established with hen's Kappa Coefficient. The association between PSG measurements and the total score of KSS was assessed using Pearson Correlation Coefficients. The diagnostic parameters of the KSS were calculated against the OSA. The receiver-operating characteristic (ROC) curve analysis was conducted to measure the association between the KSS results (Sleepy vs. non-sleepy) and the PSG parameters including AHI and ODI (continuous variables). The accepted significance level for all tests was 5% and statistical analyses were performed using IBM SPSS 28.0 for Windows SPSS Inc., Chicago, Illinois, USA.

RESULTS

The demographic and clinical characteristics of the study participants have been presented in Table 2. Proportion of the obesity was significantly different between the participants with OSA and those without OSA. Although the participants with OSA had a higher BMI, and SBP and had a larger waist circumference compared to the patients without OSA, those differences were not significant. As expected, the PSG parameters were significantly different between the two groups, per protocol.

Figure 2A illustrates that the majority of the study population reported a high level of alertness while only 3 participants rated themselves as sleepy on the KSS before driving performance at baseline. Following the simulator task performance, 11 cases were classified as sleepy and 2 cases as very sleepy according to KSS. The proportion of the participants with alertness decreased whereas the proportion of sleepy patients increased between two tests. McNemar's test result showed that the proportion of sleepiness was significantly different between the two tests (p=0.022).

As clearly illustrated in Figure 2B, in the whole study population, the total KSS score after driving performance was significantly higher than the total scores before the task, indicating the sleepiness level increased during driving (p= 0.021). In line with this result, there was a significant increase in the number of OSA patients after fifty minutes of driving (p= 0.022). However, no difference was found in the patient group with no OSA (p= 0.66). No significant between-group differences have been found regarding total KSS scores before and after the driving task (p= 0.37, p=0.99, respectively, data not shown).

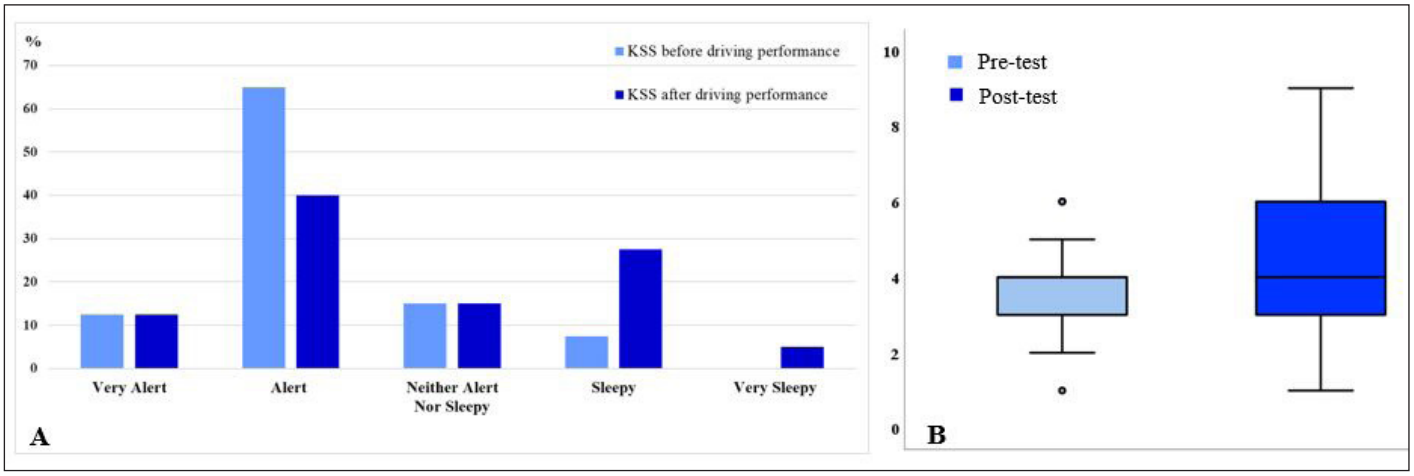

Figure 2. (A) Proportion of the participants' responses on the KSS before and after driving. task. **(B)** Distributions of the total KSS score.

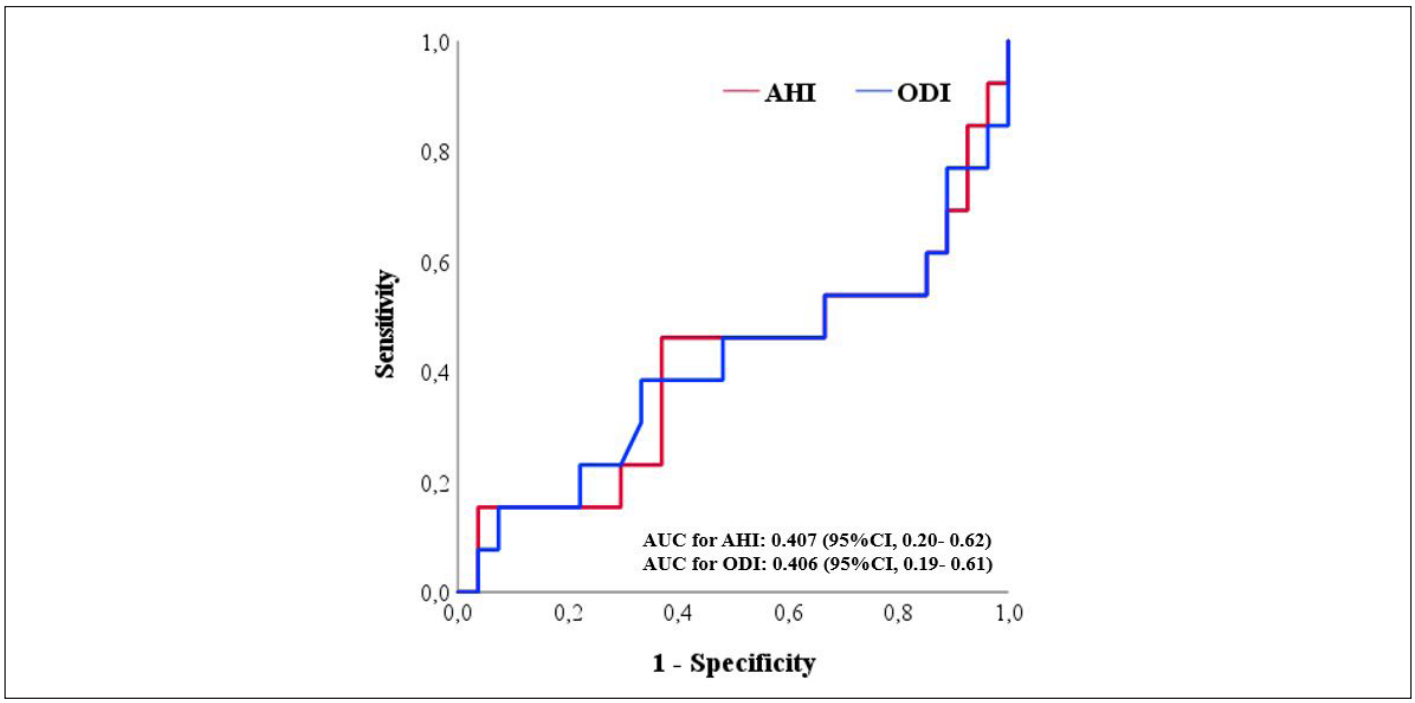

Figure 3. Receiver-operating characteristic curve of association between the KSS (with and without sleepiness) and the severity of OSA measured with AHI and ODI.

Table 2. Baseline characteristics of the study population.

	AHI ≥15 (N=29)	AHI <15 (N=11)	p
Demographics			
Age, yrs	45.1 (41.9-50.4)	45.1 (36.8-53.3)	0.72
BMI, kg/m^2	32.7 (28.9-34.3)	28.7 (23.8-32.1)	0.13
Marital Status, %	82.8	90.9	0.51
Obesity , %	67.9	28.6	0.05
Neck Circumference,cm	42.0 (41.0-44.0)	42.0 (40.0-45.0)	0.51
Waist Circumference, cm	109.5 (100.3-117.0)	102.5 (95.5-106.5)	0.36
Hip Circumference, cm	106.5 (103.0-114.8)	109.5 (100.8-112.3)	0.84
Smoking Status, %	43.8	72.7	0.36
Alcohol use, %	14.3	27.3	0.34
Family History for Snoring, %	69.0	72.7	0.88
Family History for OSA, %	10.7	0	0.50
Vital Signs			
SBP	123.0 (111.5-129.0)	119.0 (110.3-136.3)	0.54
DBP	80.0 (71.5-86.0)	84.0 (72.5-89.8)	0.43
Heart Rate	80.0 (74.0-96.0)	81.0 (69.0- 91.0)	0.56
SpO_2 (%)	98 (97-98)	98 (98-99)	0.08
PSG characteristics			
TST			
AHI	34.6 (18.4-47.9)	8.6 (6.4-11.0)	> 0.001
ODI	28.8(13.8-35.3)	5.4 (3.4-6.5)	> 0.001
Delta Sleep	68.0 (51.8- 91.0)	101.0 (78.5-126.0)	> 0.001
Rem Sleep	71.0 (48.0-83.5)	76.5 (64.0-106.0)	0.03
Comorbidities			
Allergy, %	14.3	9.1	0.56
Dyspnea, %	34.5	18.2	0.27
Asthma/COPD, %	7.1	0	0.51
Hypertension, %	17.9	9.1	0.44
Angina pectoris, %	6.9	9.1	0.63
AMI, %	0	9.1	0.27
PCI/CABG, %	6.9	0	0.52
Cardiac disease, %	6.9	0	0.52
Arrhythmia, %	6.9	9.1	0.63
Hyperlipidemia , %	10.3	9.1	0.70
Diabetes Mellitus, %	3.4	9.1	0.47
Neurological Disorder, %	3.4	9.1	0.47

Abbreviations; **AHI,** apnea-hypopnea index; **AMI,** acute myocardial infraction; **BMI,** body mass index; **CABG,** coronary artery bypass grafting; **ODI**, oxygen desaturation index, **PCI** percutaneous coronary intervention; **TST,** total sleep time; **SpO_2,** oxygen saturation

Table 3. PSG characteristics of the taxi drivers with sleepiness *vs* without sleepiness.

	Taxi Drivers with Sleepiness (N=13)	Taxi Drivers without Sleepiness (N=27)	p
TST	396.0 (339.5-422.5)	399.0 (358.0 – 424.0)	0.95
AHI	17.3 (8.2-38.7)	22.1 (15.7-44.5)	0.36
ODI	11.7 (5.3-31.2)	16.9 (10.1-30.3)	0.35
Delta Sleep	82.0 (44.5-104.5)	78.8 (57.5-103.3)	0.84
REM Sleep	72.0 (62.0-86.0)	71.5 (51.0-85.0)	0.73

Abbreviations: **AHI,** apnea hypopnea index; **ODI,** oxygen desaturation index; **REM,** repeat eye movements; **TST,** total sleep time.

Regarding the KSS classification, the patients with EDS had lower AHI, ODI, and longer total sleep time (TST) while having a shorter time in Delta sleep compared to the patients without sleepiness. However, none of those differences was significant. Furthermore, the time spent in REM sleep was also similar between the two groups (Table 3). No significant association was found between the total KSS scores, reported after the driving task, and the AHI, ODI, TST, time spent in Delta, and REM sleep (Pearson Correlation: 0.048, 0.054, -0.129, -0.079 and -0.044; p: 0.77, 0.74, 0.43, 0.63 and 0.79, respectively).

Based on the PSG, 7 (24.1%) patients with EDS were found to have AHI ≥15 events/h and 6 (54.4%) patients with sleepiness had AHI below 15 events/h. Corresponding numbers for the patients without EDS were 22 (75.9%) and 5 (45.5%), respectively. Kappa test statistic was calculated as -0.21 (p= 0.07), indicating a very weak agreement between OSA and KSS results. Diagnostic values of the KSS, including the sensitivity, specificity, accuracy, and positive and negative predictive values, were calculated as 24.14%, 45.5%, 46.6%, 53.9% and 30.0, respectively. Those values confirmed a weak diagnostic utility of the KSS for the OSA diagnosis.

The ROC curve of the association between the KSS (sleepy vs. non-sleepy) and the continuous AHI as well as ODI values have been demonstrated in Figure 3. The area under the curve was 0.57 (95% CI 0.39 – 0.74) for the AHI and 0.56 (95% CI 0.39 – 0.73) for the ODI, confirming a very poor performance of the KSS scores to predict the OSA severity.

DISCUSSION

The main finding of the current study is that the KSS is not associated with the severity of OSA indices in male taxi drivers. Although a fifty-minute driving simulator task enhanced the sleepiness levels of the taxi drivers, the PSG variables including TST, time spent in delta sleep and REM sleep, as well as AHI and ODI were not different between sleepy and non-sleepy drivers; and those variables were not associated with the drivers' sleepiness levels. Furthermore, the agreement between the OSA and the KSS was weak. In line with those results, the sensitivity, specificity, and accuracy values as well as the positive and negative predictive values provided evidence of poor performance of the KSS to screen OSA severity (24.14%, 45.5%, 46.6, 53.9%, and 30.0%, respectively).

This is the first study examining the association between KSS and OSA indices in a sleep clinic OSA population including taxi drivers. The data regarding the KSS in the clinical population is scarce. Previously, Wong et al. examined the effect of a forty-hour driving simulator task on the total KSS scores comparing OSA patients with controls [17]. According to their results, the patients with OSA had higher sleepiness levels than the patients without OSA at baseline. Nevertheless, the change in total KSS level was not significantly different between the OSA patients and the controls [17]. In the present study, there was no significant difference in the total KSS score between OSA groups at baseline. A possible argument could be that OSA patients included in the study conducted by Wong et al [17] had more severe OSA (Mean AHI= 49.8 events/hour) than the participants included in the present study (Mean AHI= 22.1 events/hour). Furthermore, we found a significant difference between the total KSS score at baseline and after the driving task within the OSA, while Wong et al [17] reported the change in KSS was not significantly different between the OSA groups. It could be explained as a regression to the mean since the OSA patients in the study of Wong et al rated their sleepiness as already high at baseline [17].

Although we found a significant increase in the KSS score after a fifty-minute drive in OSA patients, this result does not support the argument that the patients with OSA are more vulnerable to the EDS measured by the KSS than the controls. Therefore,

it needs to be confirmed in a larger sample since no association has been found between the KSS and OSA severity indices.

Sleepiness can be defined as an inability to maintain wakefulness and alertness during the day [16]. It is associated with a loss of alertness and is considered to be a consequence of sleep fragmentation and adversely affects functioning, mood, cognition, productivity, and quality of life [18,19]. It affects a large part of the population and usually increases the risk of accidents. It has been suggested that 95% of the MVAs result from driver-related factors including fatigue and sleepiness. In recent years, a growing body of literature has paid particular attention to sleepiness since up to 20% of MVAs have been associated with sleepiness, especially on monotonous roads like [20, 21]. With the awareness of OSA as a risk factor for MVAs, several international strategies have been developed to identify the drivers with high-risk for sleepiness and OSA [3]. According to the updated report of the American Thoracic Society, an individual with moderate to severe daytime sleepiness can be classified as high-risk driver and should be initially evaluated for suspected OSA [22]. The legislation regarding the driving license and OSA was updated not only in Europe [23] but also in Turkey [3]. A full-night Polysomnography (PSG), a gold standard for OSA diagnosis, was recommended regarding commercial driver-license applicants who have symptoms of witnessed apneas and/or daytime sleepiness, snoring and for those with BMI >25 kg/m^2 before getting a license [3]. Given the long waiting list in public hospitals and the limited number of sleep centers, a full-night PSG for OSA diagnosis is not feasible in Turkey. This raises a need for the development of an alternative screening tool to identify a patient with high risk as well as a patient who would unnecessarily undergo PSG when the gold standard is very expensive and not feasible. More specifically, it seems that cheap, feasible, and reachable alternatives are needed and one such is the KSS.

As aforementioned, the KSS is a one-dimensional Likert scale to measure subjective levels of sleepiness. Several studies have shown that there is a high positive intra-individual correlation between KSS scores and alpha-theta activity in the electroencephalogram (EEG) as well as behavioral variables. Moreover, it was demonstrated that falling asleep at the wheel during the simulator task was preceded by an enhanced score on the KSS. Previously, the KSS has been found a reliable tool to measure subjective levels of sleepiness in different types of studies including shift work [24, 25] jet lag [26], attention and performance [12, 27, 28] and driving abilities [29-31]. The difference between our results and those studies might be due to the type of study population. The present study includes participants from the sleep clinic cohort rather than the participants in the experimental settings. Further research is needed to evaluate the utility of the KSS for the assessment of sleepiness in the clinical population.

Limitations

There are several limitations of the present study. First, the current sample consists of male taxi drivers who work 24 hours of shift and 6 or 7 days a week. The sleep pattern for other shifts might vary. Therefore, the generalizability of the findings to non-professional drivers would be limited. Second, assessing sleepiness using a self-rated questionnaire is open to bias since it might be influenced the perceived well-being state of the subject. Moreover, the taxi drivers in the present study might likely underestimate the severity of the sleepiness level for legal issues. Third, no objective measurement of sleepiness such as maintenance of wakefulness test or we did not measure physiological response to sleepiness using EEG recordings. These aspects need to be considered in future studies.

CONCLUSIONS

The present Karolinska Sleepiness Scale seems to be a weak screening tool to identify an individual with a high risk of obstructive sleep apnea. Objective measurements are warranted for a more precise evaluation of excessive daytime sleepiness in professional drivers to predict the high risk of obstructive sleep apnea.

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Author Contributions: Conception: YC - Design: YC -Materials: YC - Data Collection and/or Processing YC - Analysis and/or Interpretation: YC - Literature: YC- Review: YC Writing: YC.

Ethical Approval: Koç University Committee on Human Research approved the study protocol (2020. 292.IRB2.083; 19 June 2020)

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Original Research

Three-Dimensional (3D) Morphometric Analysis of Plegic and Healthy Feet of Patients with Stroke

Mehmet Karagulle[1], Yilmaz Yıldırım[2], Umut Ozsoy[2], Lutfiye Bikem Suzen[3], Hatice Ikızler May[4]

[1] Department of Physiotherapy, Antalya Bilim University, Vocational School of Health Services, Antalya Turkey
[2] Department of Anatomy, Akdeniz University, Faculty of Medicine, Antalya, Turkey
[3] Department of Anatomy, Antalya Bilim University, Faculty of Dentistry, Antalya, Turkey
[4] Department of Physical Medicine and Rehabilitation, Antalya Atatürk State Hospital, Antalya, Turkey

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Correspondence
Mehmet Karagülle
Address: Antalya Bilim University, Vocational School of Health Services, Physiotherapy, Antalya, Turkey
Email: mehmet.karagulle@antalya.edu.tr

ABSTRACT

Objective: This study aimed to quantitatively assess the changes in foot morphology in stroke patients using 3D scanning and focused on parameters like foot volume, area, and the root mean square difference (RMS) values. The objective was to enhance our understanding of post-stroke foot morphology and its potential relevance for rehabilitation, especially in designing orthotic supports and specialized footwear for stroke patients.

Methods: Our study involved fourteen right hemiplegia patients and twenty healthy subjects. Stroke patients were assessed using international scales. We utilized a 3D scanning device to digitize and examine the differences in foot morphology between hemiplegic and healthy subjects, analyzing the data on a computer platform.

Results: In the context of post-stroke individuals with hemiplegic feet, our morphometric analysis revealed notable differences in foot area and foot volume when compared to their healthy counterparts. These distinctions extended to linear measurements encompassing foot length, foot width, instep height, bimalleolar width, and ball width. Significantly, RMS exhibited a substantial increase in the patient cohort compared to the healthy group ($p<0.05$). Our investigation also established correlations between these standing morphometric parameters and RMS alterations, with noteworthy coefficients for various parameters: RMS(Foot Length Difference, 0.41), RMS(Foot Width Difference, 0.45), RMS(Instep Height Difference, 0.58), RMS(Ball Width Difference, 0.58), RMS(Bimalleolar Width Difference, 0.19), RMS(Volume Difference, 0.74), and RMS(Area Difference, 0.62).

Conclusion: This study suggests incorporating RMS values as a novel parameter in the evaluation process. We anticipate that these findings will have practical implications, particularly in designing orthotic supports, specialized footwear for stroke patients, and the formulation of tailored rehabilitation programs within clinical settings.

Keywords: Stroke, 3D surface scanning, Plegic foot, Foot morphology

INTRODUCTION

Stroke is a prevalent and medically significant condition characterized by a high incidence rate, substantial mortality, and the potential for severe disabilities, if not fatal [1]. Among the most frequently encountered complications in stroke patients is the functional impairment of their affected extremities, leading

to a condition known as hemiplegia, which manifests as motor deficits affecting both the upper and lower limbs [2].

Stroke patients often experience difficulties related to stepping and exhibit atypical gait patterns [3]. While variations exist in the presentation of atypical gait among individual patients, common features include diminished balance reactions and reduced weight-bearing capacity on the affected side during different phases of walking. Achieving full functionality in the initial base contact and stepping phases of walking proves challenging due to factors such as muscle atrophy or spasticity within the foot, hindering the normal function of walking-related muscles [4, 5].

Various international scales are employed in managing stroke patients to facilitate effective treatment, monitor recovery progress, and make informed decisions regarding patient needs. Notable scales include the Functional Independence Measure (FIM), Six Minute Walk Test (6MWT), Berg Balance Scale (BBS), Functional Ambulation Classification (FAC), and Modified Ashworth Scale (MAS) [6].

The temporal aspect is crucial in stroke recovery, as the trajectory varies across time intervals [7]. One commonly utilized framework for assessing recovery stages is the Brunnstrom healing stages, which categorize stroke recovery into seven distinct phases [8].

Morphometric measurements of the foothold are critical in evaluating their suitability for shoe design, orthotic support, and footwear. Distinctions between right and left feet should be carefully considered in equipment designs for stroke patients [9]. The evaluation of foot morphology traditionally relies on various platforms and digital calipers [10, 11]. However, the advent of 3D analysis, driven by advancing technology, has expanded its utility across various domains. Utilizing 3D analysis in foot measurements allows for determining numerous parameters, with 3D browsers emerging as a novel technology for visualizing foot dimensions, encompassing measurements such as length, width, and height, among others [12-14]. Notably, the accuracy of measurement outcomes in traditional digital caliper methods is significantly influenced by potential localization errors [15].

Using the 3D scanning method in research has consistently demonstrated high reliability in standing morphological measurements, as evidenced by prior studies [12, 16]. Lee et al. [12] compared 3D scanning and traditional measurement techniques, concluding that the 3D method exhibited superior reliability.

Ambulation is a pivotal requirement for stroke patients and is crucial to their recovery and psychological well-being [17]. Effective shoe design for individuals post-stroke is vital in characterizing their walking patterns.

Ankle Foot Orthosis (AFO) is an essential intervention to address musculoskeletal issues, facilitating the restoration of standard walking mechanics [18]. Appropriate AFO support can significantly enhance walking independence among stroke patients [19]. Traditional AFO design typically involves multiple materials and casting, resulting in an extended production timeline. However, this approach may limit the mechanical adjustments required to meet individual patient needs [20, 21].

In the context of our research, our primary objective was to perform a quantitative assessment of post-stroke foot modifications, employing the three-dimensional (3D) scanning technique. In addition to traditional linear measurements, our study aimed to expand the existing body of knowledge by examining the relationships among foot volume, foot area, and root mean square difference values (RMS), which serve as valuable indicators of inter-foot asymmetry. This research contributes to a deeper understanding of post-stroke foot morphology and its implications for rehabilitation and orthotic support design.

MATERIALS AND METHODS

Ethical clearance for this investigation was duly secured from the Ethics Committee of Clinical Research at Akdeniz University, denoted by approval number 70904504/582, granted on the 26th of December 2018. All participating volunteers provided written informed consent. Our study cohort comprised seven male and seven female right hemiplegia patients. Additionally, measurements were obtained from thirty-four individuals, comprising ten male and ten female volunteers in the healthy control group, to ensure age-matching.

Inclusion Criteria: Right hemisphere stroke dominance (ensuring uniformity among both patients and the control group); specific reference to Brunnstrom Stages 3 or 4; the absence of any pre-existing foot trauma or post-stroke foot trauma; and the absence of any open wound that might potentially influence

foot measurements are the inclusion criteria. These criteria were meticulously applied to ensure the homogeneity and appropriateness of the study cohort.

Exclusion Criteria: Patients who were contraindicated to take the supine position to be used during the study and those who were contraindicated to elevate the leg due to deep vein thrombosis were not included.

Scales Used in the Study

Modified Ashworth Scale (MAS): We used MAS to determine the level of spasticity. Since our study was based on the foot, we evaluated only ankle plantar flexor spasticity between "0" and "4" points.

Functional Independence Measure (FIM): We used the FIM to obtain information about the addiction and functionality status of the patients. We made scoring in two main sections within the FIM itself: motor scoring and cognitive scoring. We scored the sub-parameters under these two main headings according to the condition of the patients. Patients scored between "1" and "7" points. We first collected the scores obtained in each category separately and determined the FIM motor score and the FIM cognitive score. Then, we found the FIM total score by summing the FIM motor score and the FIM cognitive score.

Six-Minute Walk Test (6MWT): This test was carried out in a controlled manner on walking bars prepared for patients. Extra precautions have been taken to prevent patients from falling. Many patients rested regularly by sitting in a chair and then continued walking. At the end of 6 minutes, the distance he took was recorded on the form.

Functional Ambulation Classification (FAC): We classified the patients according to the primary motor skills required for functional ambulation. In this classification, we gave the patients scores between "0" and "5" points. While evaluating the ambulation, we evaluated by taking the necessary precautions against the risk of falling.

Berg Balance Scale (BBS): We evaluated balance with BBS in our hemiplegic patients. We gave 14 instructions to the patients and evaluated their balance in these instructions by scoring between "0" and "4" points. Afterward, we determined the BBS total score by adding up the scores obtained in each directive.

Foot Evaluation Procedure with 3D Method

Each volunteer's foot was scanned using a 3D scanner. Scanning was supine, with the feet protruding from the bed just above the ankle level (Figure 1). After the patients and healthy volunteers in the control group were supine, a full rotation was made around the foot with the scanner. This way, images of both the right and left feet were taken. Each foot scan took about 40 seconds. The 3D scanned images were subjected to a series of processing in STL format with Artec Studio 11 software (version 11.2.2.16; licensed by Artec Group, Luxembourg).

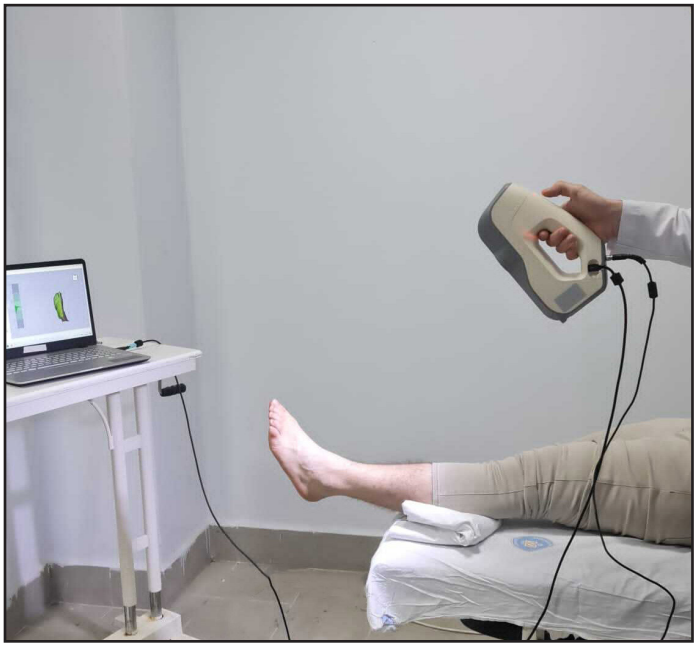

Figure 1. 3D foot scan position.

Image Processing

First, global registration was made, and then the surface was created with sharp fusion. This image was cropped from the malleolus level. After that, A working image was created by applying a small object filter and mesh simplification. Then, the measurement process was started. For linear measurements, clicking on the measurement tab and selecting two points is necessary. The distance measurements between these two points were made by clicking make another sequentially. The volume and area measurement was made from the measurement section. RMS (Mean Square Root Difference Value): A statistical criterion used to measure the magnitude of changing quantities, the square root of the mean value of the square function of the instantaneous values is the RMS value. Differences between right and left feet were calculated using RMS. After scanning both feet, a mirror image of one foot was taken.

In order to calculate the RMS value, both images should be similar to each other as a protocol. Therefore, it is necessary to create a mirror image using Autodesk Netfabb software (Netfabb, Parsberg, Germany, Free trial version) and then transfer it to Artec Studio 11 software [22]. In our study, a mirror image of the left foot was taken.

Two comparable images are superimposed to analyze asymmetry. The RMS value is used to assess shape differences quantitatively. This number represents the difference between two 3D surfaces and illustrates how different or similar the compared shapes are. Higher values represent more diversity, while lower values represent more similar shapes than the compared one. The program produces maps of color deviation. These maps offer a quick analysis using color to highlight the differences between the two surfaces. Blue, which represents a negative distance, is replaced by red, which represents a positive distance, on the map. Green indicates that the difference between the surfaces is almost zero at this point [23]. In our research, the left and right foot mirror images were superimposed, and color deviation maps were created (Figure 2).

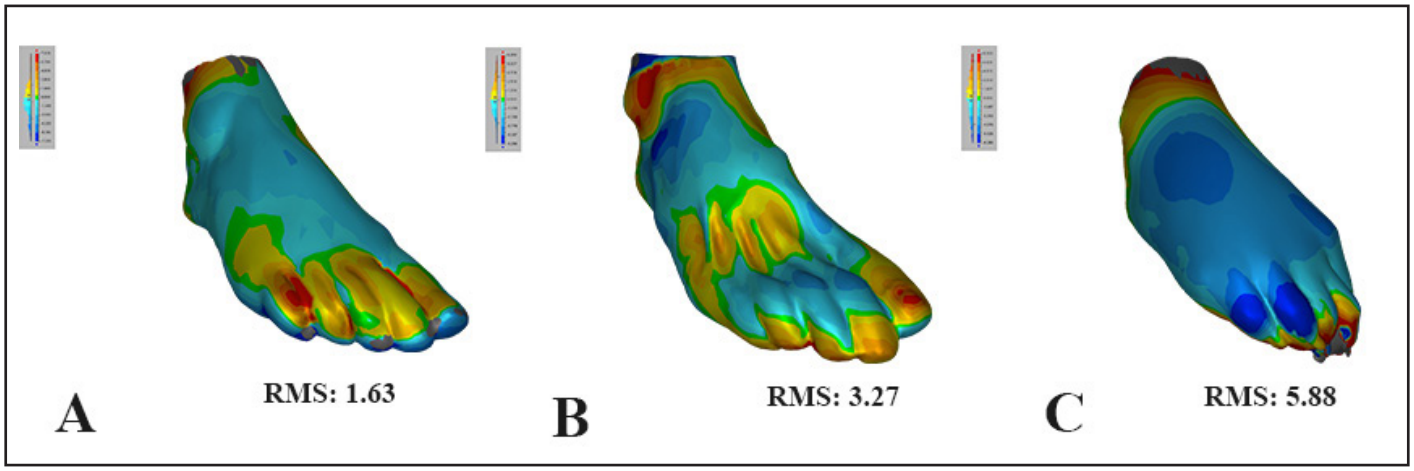

Figure 2. Color distance maps and RMS values. Green areas indicate no change. It shows a positive change as the color changes from green to yellow and red. As the darkness of the blue increases, it changes in the negative direction (A- Low RMS, B- Medium RMS, C-High RMS).

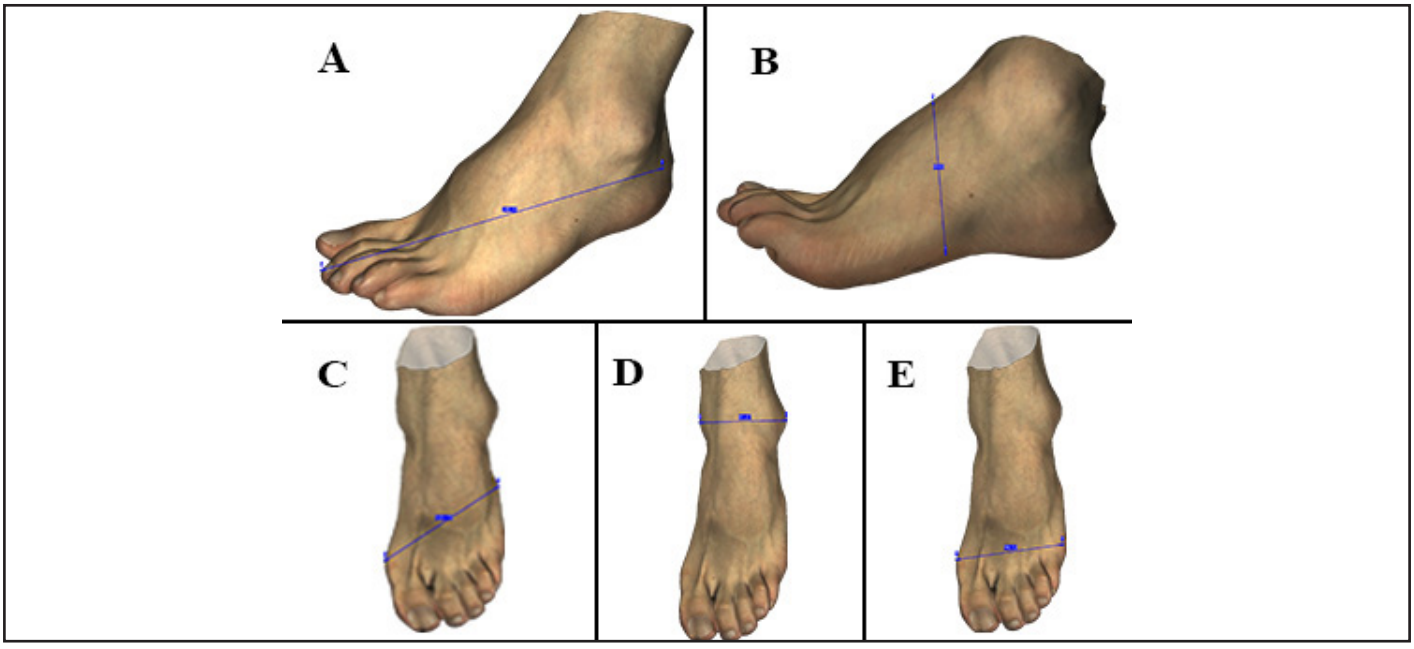

Figure 3. Linear measurements (A: Foot length, B: Instep height, C: Foot width, D: Bimalleolar width, E: Ball width)

Morphological Measurements

Foot length, foot width, instep height, bimalleolar width, and ball width were measured linearly. In addition to these, foot area and foot volumes are also morphological measurements provided by 3D scanning.

Foot length: The distance measured along the axis of the foot between the most posterior point of the foot (pterion) and the tip of the second toe (Figure 3-A).

Instep height: It is the distance between the sole and the vertical top of the dorsum of the foot (Figure 3-B).

Foot width: It is the distance between the most protruding points of the foot, medially and laterally (Figure 3-C).

Bimalleolar width: The distance between the most protruding points of the medial and lateral malleolus (Figure 3-D).

Ball width: The distance measured between the first metatarsal head's most protruding point and the fifth metatarsal head (Figure 3-E).

Foot area: The total area of the foot was calculated from the malleolus level.

Foot volume: The total volume of the foot was calculated from the malleolus level.

Statistical Analysis

SPSS 23.0 package program was used in the analysis. The assumption of normal distribution was checked with the Shapiro-Wilk test. T-test was performed if normal distribution was provided, and the Mann-Whitney U test was performed if not. Spearman correlation test was used because there was no normal distribution in the correlation. In statistical data, $p<0.05$ was considered statistically significant.

RESULTS

Our patients are fourteen right-stroke cases, seven women and seven men. We evaluated the general condition of selected patients in these groups using internationally used scales such as FIM, MAS, BBS, 6MWT, and FAC. These scales provided information about the patient's general condition (Table 1).

3D Scan Findings

Morphometric measurements of the foot were made on both feet in both the control group and the stroke patient group. First, the general averages were taken, and then the difference analysis process was started. In order to examine the significance of the study, the difference between the right and left feet was taken.

The dominant side is the right side in our study's control and patient group volunteers. While taking the difference operation, all the parameters of the control group were examined first, and with minor exceptions, the numerical magnitude was observed in the parameters of the right feet compared to the left feet.

Table 1. Scale results

		Count	Column N %	Valid N	Mean	Standard Deviation	Median	Percentile 25	Percentile 75
GENDER	male	7	50.0%						
	female	7	50.0%						
MAS (0-4)	1	6	42.9%						
	1+	5	35.7%						
	2	3	21.4%						
FIM MOTOR (0-91)				14	63.93	11.73	66.50	60.00	71.00
FIM TOTAL (0-126)				14	93.07	14.00	97.00	87.00	100.00
FAC (0-5)				14	3.21	1.31	3.50	3.00	4.00
BBS (0-56)				14	29.29	11.36	32.50	25.00	35.00
6MWT (METER)				14	47.00	21.71	55.50	40.00	60.00

Therefore, the difference operation is obtained by subtracting the left foot's numerical parameters from the right foot's numerical parameters. For standardization in our study, only right-stroke patients were included in the study, and the measurement parameters of the healthy left foot were subtracted from the measurement parameters of the dominant right plegic foot, and the difference process was created. The overall mean values for linear measurements are given in Table 2, and the difference values are given in Table 3. Mean values and difference values of area, volume, and RMS measurements are given in Table 4.

After taking the differences in the parameters, their significance was examined. After the statistical analysis, our study was found to be significant regarding the change in the difference value parameters ($p<0.05$). In other words, when the difference between the right and left feet of the control group and the difference between the right and left feet of the stroke group were examined, the right foot of the stroke group decreased significantly compared to the left foot (Tables 5 and 6).

There was no significant difference between the linear measurements of the left feet of both groups. In addition, when the measurements of the left feet of both groups, such as area and volume, are examined, there is no significant difference. This means that we created a comparison group that is close to each other regarding the left feet of our volunteers (Tables 5 and 6).

Table 2. Linear measurement results of right and left feet

		GROUP					
		Valid N	**Mean**	**Standard Deviation**	**Median**	**Percentile 25**	**Percentile 75**
Right foot length (cm)	Control	20	23.06	1.64	22.50	21.76	24.62
	Stroke	14	22.21	1.94	21.54	20.79	22.72
Left foot length (cm)	Control	20	22.85	1.67	22.37	21.42	24.42
	Stroke	14	22.74	1.65	22.52	21.63	23.22
Right foot width (cm)	Control	20	9.22	.51	9.11	8.79	9.70
	Stroke	14	8.94	0.75	9.01	8.38	9.50
Left foot width (cm)	Control	20	9.17	0.53	9.10	8.70	9.61
	Stroke	14	9.15	0.73	9.17	8.42	9.67
Right instep height (cm)	Control	20	8.11	0.88	8.34	7.74	8.55
	Stroke	14	7.43	0.56	7.57	7.12	7.83
Left instep height (cm)	Control	20	8.08	0.83	8.27	7.75	8.52
	Stroke	14	7.60	0.57	7.64	7.29	8.12
Right ball width (cm)	Control	20	8.23	0.81	8.03	7.55	8.54
	Stroke	14	8.07	0.66	7.89	7.60	8.23
Left ball width (cm)	Control	20	8.16	0.81	7.93	7.50	8.73
	Stroke	14	8.26	0.63	8.15	7.82	8.51
Right bimalleolar width (cm)	Control	20	7.32	0.48	7.25	6.97	7.65
	Stroke	14	7.08	0.68	6.93	6.50	7.81
Left bimalleolar width (cm)	Control	20	7.28	0.51	7.27	6.89	7.60
	Stroke	14	7.24	0.81	6.99	6.51	8.13

When we examined the right feet of both groups, there was no significant change in linear measurements in foot width, ball width, and bimalleolar width. However, there was a significant ($p<0.05$) change in instep height and a statistically marginal change in foot length ($p=0.61$). This means that the plegic feet are remarkably reduced in length and height. When the evaluation was made between the right and left foot, the RMS values were checked to see this change. A significant difference was found between the RMS values of the feet of healthy volunteers and the RMS values of the patients with stroke (Table 5) in terms of the RMS value, which is one of the most critical aspects of our study, in which the difference between the two feet is evaluated ($p<0.05$).

Correlation Evaluation

We examined the correlation between the standing difference values and the RMS. We found significant correlations between the morphometric difference values measured in the standing position and the change in the RMS value. RMS (Foot Length Difference, r =0.41), RMS (Foot Width Difference, r=0.45), RMS (İnstep Height Difference, r =0.58), RMS (Ball Width Difference, r =0.58), RMS (Volume Difference, r =0.74), RMS (Area Difference, r =0.62). This proves that the RMS value is a clinical finding that can quantitatively show the change in the foot. There was no significant correlation between only bimalleolar width difference and RMS (r =0.19). This is because the measurement of bone structures is at the forefront in the measured distance between the malleolus (Table 7).

Table 3. Difference values between right feet and left feet

		GROUP					
		Valid N	**Mean**	**Standard Deviation**	**Median**	**Percentile 25**	**Percentile 75**
Foot length difference (cm)	Control	20	0.14	0.24	0.11	0.05	0.25
	Stroke	14	-0.53	0.78	-0.34	-0.83	-0.03
Foot width difference (cm)	Control	20	0.06	0.17	0.07	0.04	0.19
	Stroke	14	-0.21	0.16	-0.19	-0.37	-0.09
Instep height difference (cm)	Control	20	0.03	0.16	0.04	0.00	0.13
	Stroke	14	-0.17	0.15	-0.10	-0.28	-0.06
Ball width difference (cm)	Control	20	0.07	0.14	0.07	0.05	0.12
	Stroke	14	-0.19	0.10	-0.20	-0.28	-0.08
Bimalleolar width difference (cm)	Control	20	0.04	0.10	0.03	-0.01	0.08
	Stroke	14	-0.16	0.21	-0.09	-0.32	-0.05

Table 4. Volume and area of the right and left feet and RMS value with the area and volume difference values of the feet

		GROUP					
		Valid N	**Mean**	**Standard Deviation**	**Median**	**Percentile 25**	**Percentile 75**
Right foot volume (cm^3)	Control	20	965.42	157.62	954.02	843.33	1038.80
	Stroke	14	866.81	193.44	853.63	696.20	1051.96
Left foot volume (cm^3)	Control	20	937.26	154.53	940.16	804.15	1005.53
	Stroke	14	925.39	189.75	899.44	768.15	1113.62
Foot volume difference (cm^3)	Control	20	28.16	39.43	31.71	4.31	43.05
	Stroke	14	-58.58	31.09	-49.88	-59.99	-44.13
Right foot area (cm^2)	Control	20	670.50	101.09	651.21	605.74	711.20
	Stroke	14	608.85	73.95	608.94	535.54	670.33
Left foot area (cm^2)	Control	20	642.14	73.88	633.18	579.38	684.88
	Stroke	14	653.07	79.54	674.62	586.28	713.92
Foot area difference (cm^2)	Control	20	28.36	72.18	15.30	-1.78	31.12
	Stroke	14	-44.22	32.86	-32.55	-71.99	-21.46
RMS value	Control	20	2.83	0.62	2.78	2.48	3.31
	Stroke	14	3.93	0.84	3.61	3.27	4.31

Table 5. Comparison of the mean values of the right and left feet of the control group and the stroke group and the comparison of the difference values of the feet (parameters that do not provide normal distribution)

Test Statistics[a]											
	Right foot length (cm)	**Right foot width (cm)**	**Foot width difference (cm)**	**Instep height difference (cm)**	**Right ball width (cm)**	**Ball width difference (cm)**	**Right bimalleolar width (cm)**	**Bimalleolar width difference (cm)**	**Volume difference (cm^3)**	**Area difference (cm^2)**	**RMS value**
Mann-Whitney U	86.500	109.000	29.500	21.500	125.500	14.000	112.000	47.000	13.000	9.000	38.000
Wilcoxon W	191.500	214.000	134.500	126.500	230.500	119.000	217.000	152.000	118.000	114.000	248.000
Z	-1.872	-1.085	-3.873	-4.149	-.508	-4.413	-.980	-3.258	-4.444	-4.584	-3.570
Asymp. Sig. (2-tailed)	0.061	0.278	0.000	0.000	0.612	0.000	0.327	0.001	0.000	0.000	0.000
Exact Sig. [2*(1-tailed Sig.)]	0.061	0.290	0.000	0.000	0.616	0.000	0.341	0.001	0.000	0.000	0.000

Table 6. Comparison of the mean values of the right and left feet of the control group and the stroke group and the comparison of the difference values of the feet (Parameters providing normal distribution)

Independent Samples Test									
	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
Left foot length (cm)	0.291	0.593	0.192	32	0.849	0.11136	0.57967	-1.06938	1.29210
			0.193	28.343	0.849	0.11136	0.57846	-1.07292	1.29563
Foot length difference (cm)	8.421	0.007	3.622	32	0.001	0.66571	0.18379	0.29134	1.04009
			3.111	14.746	0.007	0.66571	0.21401	0.20889	1.12254
Left foot width (cm)	0.995	0.326	0.091	32	0.928	0.01957	0.21589	-0.42018	0.45933
			0.086	22.456	0.932	0.01957	0.22806	-0.45283	0.49198
Right instep height (cm)	1.902	0.177	2.551	32	0.016	0.68171	0.26718	0.13748	1.22595
			2.760	31.741	0.010	0.68171	0.24701	0.17842	1.18501
Left instep height (cm)	1.330	0.257	1.882	32	0.069	0.48157	0.25585	-0.03958	1.00273
			2.007	32.000	0.053	0.48157	0.23992	-0.00713	0.97027
Left ball width (cm)	1.916	0.176	-0.391	32	0.698	-0.10071	0.25767	-0.62558	0.42415
			-0.408	31.506	0.686	-0.10071	0.24675	-0.60363	0.40220
Left bimalleolar width (cm)	8.664	0.006	0.147	32	0.884	0.03336	0.22739	-0.42981	0.49653
			0.136	20.225	0.893	0.03336	0.24589	-0.47920	0.54591
Right foot volume (cm^3)	2.063	0.161	1.635	32	0.112	98.61193	60.30782	-24.23107	221.45493
			1.576	24.300	0.128	98.61193	62.56963	-30.44119	227.66505
Left foot volume (cm^3)	2.622	0.115	0.201	32	0.842	11.87657	59.14136	-108.59044	132.34358
			0.194	24.290	0.848	11.87657	61.36512	-114.69482	138.44796
Right foot area (cm^2)	0.738	0.397	1.943	32	0.061	61.64214	31.72690	-2.98345	126.26773
			2.053	31.904	0.048	61.64214	30.02689	0.47212	122.81217
Left foot area (cm^2)	0.764	0.389	-0.412	32	0.683	-10.93500	26.56221	-65.04045	43.17045
			-0.406	26.765	0.688	-10.93500	26.92087	-66.19479	44.32479

Table 7. Correlation diagram

			RMS value	Foot length difference (cm)	Foot width difference (cm)	Instep height difference (cm)	Ball width difference (cm)	Bimalleolar width difference (cm)	Foot volume difference (cm^3)	Foot area difference (cm^2)
Spearman's rho	RMS value	Correlation Coefficient	1.000	-0.411	-0.451	-0.585	-0.588	-0.193	-0.745	-0.627
		Sig. (2-tailed)		0.016	0.007	0.000	0.000	0.509	0.000	0.000
		N	34	34	34	34	34	34	34	34
	Foot length difference (cm)	Correlation Coefficient	-0.411	1.000	0.470	0.524	0.508	0.197	0.505	0.607
		Sig. (2-tailed)	0.016		0.005	0.001	0.002	0.500	0.002	0.000
		N	34	34	34	34	34	34	34	34
	Foot width difference (cm)	Correlation Coefficient	-0.451	0.470	1.000	0.581	0.732	0.060	0.617	0.635
		Sig. (2-tailed)	0.007	0.005		0.000	0.000	0.839	0.000	0.000
		N	34	34	34	34	34	34	34	34
	Instep height difference (cm)	Correlation Coefficient	-0.585	0.524	.581	1.000	.770	.339	.816	.791
		Sig. (2-tailed)	0.000	0.001	.000		.000	.236	.000	.000
		N	34	34	34	34	34	34	34	34
	Ball width difference (cm)	Correlation Coefficient	-0.588	0.508	0.732	0.770	1.000	0.022	0.734	0.712
		Sig. (2-tailed)	0.000	0.002	0.000	0.000		0.940	0.000	0.000
		N	34	34	34	34	34	34	34	34
	Bimalleolar width difference (cm)	Correlation Coefficient	-0.193	0.197	0.060	0.339	0.022	1.000	-0.128	0.190
		Sig. (2-tailed)	0.509	0.500	0.839	0.236	0.940		0.662	0.515
		N	34	34	34	34	34	34	34	34
	Foot volume difference (cm^3)	Correlation Coefficient	-0.745	0.505	0.617	0.816	0.734	-0.128	1.000	0.935
		Sig. (2-tailed)	0.000	0.002	0.000	0.000	0.000	0.662		0.000
		N	34	34	34	34	34	34	34	34
	Foot area difference (cm^2)	Correlation Coefficient	-0.627	0.607	0.635	0.791	0.712	0.190	0.935	1.000
		Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.515	0.000	
		N	34	34	34	34	34	34	34	34

DISCUSSION

Our study's utilization of the 3D scanning technique conferred a notable advantage by facilitating a more comprehensive analysis. In contrast to the conventional approach employing calipers and platforms for measurements, the 3D scanning method offered the capability to conduct multiple measurements within the same timeframe. Consequently, this approach enabled the replication of measurements and permitted the assessment of parameters such as volume, area, and RMS, which are otherwise unattainable through traditional methodologies. [12, 21, 23].

The application of 3D scanning affords flexibility in conducting imaging procedures, permitting data acquisition at the researcher's discretion, with the frequency of scans being adaptable. In contrast to techniques focused solely on analyzing select points on the dorsal surface, the 3D methodology comprehensively assesses the back surface by scrutinizing approximately thirty thousand data points (vertex). Notably, the hand-held scanner can be employed in hospital and polyclinic settings, obviating the necessity for specialized laboratory conditions. Furthermore, the device facilitates the examination of patients in their preferred bodily positions, enhancing clinical versatility and patient comfort. [22].

Surface scanning presents a significant innovation by generating colored surface deviation maps, which offer a valuable tool for identifying alterations and deformation regions within the foot. This map enables a streamlined visual assessment of the extent of deformation, quantified as the RMS value, thereby facilitating meaningful comparisons and analytical insights.[23].

The image processing process of the 3D method takes a relatively long time. In our study, it took an average of 10 minutes to process the image of a foot. This image processing can be learned quickly, but it takes time to gain experience. As experience increases, image processing can be faster [22, 23].

Several 3D scanning investigations have previously explored foot morphology aspects within the existing literature. These studies have predominantly concentrated on assessing disparities in foot structure between genders, employing parameters such as foot length, foot width, bimalleolar width, and instep height as crucial metrics. Moreover, findings from these studies have been instrumental in informing endeavors related to footwear design and the development of supplementary equipment, notably AFO, contributing to advancements in the field. [24-27].

In a study conducted by Saghazadeh et al.[26] the feet of 151 male and 140 female healthy elderly Japanese volunteers underwent comprehensive 3D scanning. The principal objective of this investigation was to employ 3D scanning technology to assess and discern disparities in foot morphology between males and females. The study's findings unequivocally underscored the observation that, on average, male foot dimensions were appreciably more prominent than their female counterparts.

In the research conducted by Chiroma et al. [24], which involved a comparative analysis of foot anthropometry among individuals aged 18-45 in Nigerian society, noteworthy findings were observed. Specifically, their study revealed that male participants exhibited notably higher numerical values in measurements related to instep height, foot length, and foot width when compared to their female counterparts.

Li et al. [13] employed a 3D scanning methodology to investigate foot anthropometric measurements in the context of elderly individuals in Hong Kong, specifically focusing on its implications for shoe design. Their study encompassed 49 volunteers, involving 98 feet, categorized into 26 healthy feet and 72 deformed feet based on physical examinations. Notably, our attention was drawn to the approach employed in Li's study, which primarily relied on physical examinations for classification. We assert that the exclusive reliance on physical examination may introduce subjective elements into the dataset about foot conditions. In contrast, in our investigation, a deliberate effort was made to enhance objectivity in selecting healthy volunteers. We rigorously established inclusion criteria, deliberately choosing fully healthy, non-deformed feet as the basis for comparison. Furthermore, within the patient group, we adhered to internationally recognized scales to ensure that individuals at equivalent levels of impairment were included in our study cohort, further enhancing our findings' comparability and scientific rigor.

In the study conducted by Liu et al. [25], a cohort comprising 12 stroke patients underwent 3D foot scans, with the primary objective of employing the acquired scan data to design AFO tailored to individual patients. 3D scanning technology in this clinical context facilitated the creation of AFO designs that exhibited enhanced functionality, marking a noteworthy advancement in patient-specific orthotic interventions.

In contrast to previous 3D studies focused on foot morphology,

our present study incorporates a more comprehensive evaluation by considering key parameters such as foot volume, area, and RMS values. This holistic approach enhances the versatility of foot examination and serves as a valuable contribution to the existing literature. It is important to note that measuring area, volume, and RMS parameters necessitates a more significant investment of time and demands more expertise than conventional parameters like foot length, width, and height. However, this more nuanced assessment provides a deeper understanding of foot characteristics and has the potential to yield valuable insights for clinical and research purposes.

Using 3D scans of the feet enables the design of personalized footwear. Mickle et al. [28] observed significant foot morphology alterations in elderly individuals through 3D foot scanning, emphasizing the necessity for shoe designs that accommodate these changes. Our study similarly highlights morphological foot changes in elderly stroke patients, suggesting the potential requirement for specialized footwear. 3D scanning serves as a promising method for crafting such tailored footwear.

Yamashito et al. [29] used a smartphone to capture two-dimensional foot images and convert them into 3D representations within a computer environment. In contrast, our study directly acquired 3D images utilizing a dedicated 3D scanner. This approach affords distinct advantages, enabling precise parameter measurements such as area, volume, and RMS, which can be presented as comprehensive working data. It is noteworthy to distinguish our approach from that of Yamashito et al., who employed two-dimensional smartphone imaging and 3D reconstruction in a computer environment. In contrast, our study directly recorded 3D images using a dedicated 3D scanner, allowing for the presentation of parameters such as area, volume, and RMS as precise and comprehensive working data. This methodological distinction underscores the advantages of direct 3D scanning in facilitating a more detailed and accurate assessment of foot morphology.

However, our study does have notable limitations. It was exclusively conducted on volunteers with right hemiplegia, warranting further research encompassing a larger cohort that includes individuals with left hemiplegia to enhance the breadth of insights. Although essential, participants need to maintain stillness during the evaluation process may pose challenges for stroke patients and introduce motion artifacts, necessitating re-shooting in such instances. Additionally, due to registration difficulties, our study's limited number of patients underscores the need for future investigations with larger sample sizes to bolster the scientific literature. Furthermore, our study exclusively included patients within Brunnstrom stages 3 and 4 for homogeneity, yet exploring changes in patients with more severe or improved conditions could provide valuable insights. We hypothesize that RMS values may vary, with higher values associated with more severe atrophy or spasticity and lower values in patients in advanced recovery stages. Addressing this knowledge gap requires further studies to refine our understanding. The scarcity of existing research in this domain presents challenges regarding comparisons. Nevertheless, our study, which contrasts the hemiplegic foot with the healthy foot within stroke patients and compares both to healthy volunteer feet, generates data that can be valuable across multiple domains.

CONCLUSION

Our research offers a 3D analysis and quantitative evaluation of changes in hemiplegic feet. Linear measurements and parameters such as area, volume, and RMS present novel avenues for assessment. We anticipate that our findings will contribute to developing orthotic supports, specialized footwear design for patients, and the formulation of tailored rehabilitation programs within clinical settings.

Conflict of interest: There is no conflict of interest.

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Original Research

Bibliometric Analysis of Alveolar Ridge Augmentation Over the Last 20 Years

Serkan Yıldız[1]

[1] Department of Oral and Maxillofacial Surgery, Istanbul Aydın University, Faculty of Dentistry, Istanbul, Turkey

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Correspondence
Serkan Yıldız
Adress: Istanbul Aydın University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery
E-mail: serkanyildiz354@hotmail.com

ABSTRACT

Objective: This study aims to provide insights into the evolution and trends of academic efforts in the field of alveolar ridge augmentation through a bibliometric analysis. The objective is to assist researchers interested in future work within this domain by identifying potential areas of exploration and contributing to the field's advancement.

Methods: The bibliometric analysis encompasses publications related to alveolar ridge augmentation between 2000 and 2023, sourced from the Web of Science Core Collection database. The analysis involves various metrics and visualization tools, including Citespace, VOSviewer, and Biblioshiny, to evaluate publication patterns, journal analyses, country analyses, reference analyses, and keyword analyses.

Results: The analysis of 3,477 publications revealed a logistic growth pattern with an annual growth rate of 5.52%. Among the most commonly found document types were original articles, reviews, and editorial content. The journal analysis indicated the dominance of specific journals, with a small core journal group identified through Bradford's Law. The United States emerged as a leader in terms of publication and citation counts. Co-citation clustering unveiled evidence-based topics and the progression of research trends.

Conclusion: This bibliometric analysis sheds light on the trajectory of academic contributions in the field of alveolar ridge augmentation. It offers valuable insights for researchers considering future work by identifying potential areas for exploration and contributing to the field's progress.

Keywords: Bibliometric; Alveolar Ridge Augmentation; Grafting

INTRODUCTION

Alveolar ridge augmentation, a significant aspect of modern dental surgical practice, has evolved into a pivotal and continuously advancing field [1–3]. Enlarging the dimension or volume of the alveolar ridge on the jawbone is regarded as a critical step to ensure the successful execution of dental implantation and other dental restorative procedures. This surgical process aims to establish the necessary foundation for the secure integration of implants in cases of inadequate bone volume. Alveolar ridge augmentation not only plays a crucial role in the pre-operative and post-operative stages of the procedure but also forms a cornerstone for long-term success [4, 5].

The progression of modern medical technology and the increasing popularity of dental implants have led to a rapid surge in research dedicated to alveolar ridge augmentation [6] performing alveolar distraction osteogenesis (ADO. Presently, dental implants have become one of the most preferred restorative

options for tooth loss [7]. However, the presence of an adequate amount of bone is imperative for the successful integration of implants. This is precisely where alveolar ridge augmentation emerges as an indispensable step to facilitate proper conditions for dental implantation.

Bibliometric analysis serves as a potent tool for comprehending the quantitative and qualitative aspects of scientific research [8, 9]. The rise in the number of publications in the field of alveolar ridge augmentation has further elevated the significance of bibliometric analysis in this domain. This analytical approach aids not only in assessing the overall growth rate within the field but also in identifying specific subtopics of research, most cited studies, and influential researchers [10, 11]. Moreover, valuable insights such as the extent of leadership assumed by different countries in this field and the prominent journals serving as publication platforms can be derived through this analysis [12].

The objective of this study is to present a comprehensive overview of the literature surrounding alveolar ridge augmentation over the past two decades. Throughout this process, understanding the pace of advancements in the field and determining which areas have garnered greater attention becomes crucial in shaping the direction of future research endeavors. As alveolar ridge augmentation forms a fundamental bridge for successful dental implantation, research in this domain will continue to contribute to the expansion and progression of the discipline. In conclusion, this bibliometric analysis pertaining to alveolar ridge augmentation aims to offer a broad perspective on the strides taken in the realm of dental surgery and implantation. This analysis not only aids in comprehending the current state but also assists in identifying potential areas for future studies, thus guiding the advancement of the field.

Main Points;

- The analysis of 3,477 publications revealed a logistic growth pattern with an annual growth rate of 5.52%.
- Cluster analysis based on co-citations divided the literature into 17 topic headings.
- The largest cluster was "titanium mesh exposure (Cluster #0)" with 110 articles.
- The strongest citation burst was related to the keyword 'alveolar bone grafting'.

MATERIALS AND METHODS

Due to adhering to the principles of the Leiden Manifesto, this bibliometric analysis study is exempt from ethical approval. The Web of Science Core Collection database was utilized to retrieve publications related to alveolar ridge augmentations within the years 2000 to 2023. The search employed the following terms: "khoury technique (Topic) or urban technique (Topic) or Horizontal Ridge Augmentation (Topic) or Horizontal Bone Augmentation (Topic) or Shell technique (Topic) or Vertical Alveolar Ridge Augmentation (Topic) or umbrella technique (Topic) and Alveolar Ridge Augmentation (Should – Search within topic) and Bone Augmentation (Should – Search within topic) and Ridge Augmentation (Should – Search within topic) and Vertical Ridge Augmentation (Should – Search within topic) and Dentistry Oral Surgery Medicine (Web of Science Categories) and 2023 or 2022 or 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2014 or 2015 or 2013 or 2012 or 2011 or 2010 or 2009 or 2008 or 2007 or 2006 or 2005 or 2004 or 2003 or 2002 or 2001 or 2000 (Publication Years)."

Full records and complete reference lists of the accessed publications were downloaded in plain text format and subjected to data cleansing using Excel 2016 software. Subsequently, Citespace, VOSviewer, and Biblioshiny software [13] were employed for bibliometric analyses. In the visual representations of the data, nodes represented objects of interest such as references/authors/countries/keywords, while the lines connecting the nodes depicted relationships between pairs of nodes. The size of a node was indicative of the frequency of that element in the analysis; likewise, the thickness of the line connecting two nodes corresponded to the intensity of the connection between them.

Co-citation is a concept in bibliometrics and information retrieval that refers to the relationship between two documents based on the frequency with which they are cited together by other documents [14]. In other words, if two documents are frequently cited in the same context by other researchers, they are considered to have a co-citation relationship [15]. Co-citation analysis is often used in academic research to identify the intellectual connections between different works and to understand the relationships between authors, topics, or fields of study. Co-citation analysis can provide valuable insights into the intellectual structure of a particular research field, helping researchers identify seminal works, influential authors, and emerging trends. It is a useful tool for mapping the landscape of

academic literature and understanding the connections between different scholarly works. In this study, co-citation relationships were examined using functions of the Citespace software.

While the publication-citation numbers of the journals and their zones according to Bradford's scattering law were evaluated with Biblioshiny software [13], quartile groups were determined using Journal Citation Reports 2022. While metric properties such as keyword frequency and citation burst were obtained from Citespace software, Vosviewer software was used for visualizations.

RESULTS

General Outcomes

There were a total of 3,477 publications between 2000 and 2023. The annual publication count demonstrated logistic growth with an annual growth rate of 5.52% (Figure 1). The year 2019 had the highest number of publications with 238. Among the most common document types were 2,869 original articles, 325 reviews, 34 editorial contents, 14 editorials, and 13 meeting abstracts. The literature involved 9,694 authors, 7,590 institutions, and was published in 199 journals.

Journal Analysis

Out of a total of 199 journals, only 4 were part of the core journal group according to Bradford's Law. With 416 publications, "Clinical Oral Implants Research" held the top position in terms of publication count, followed by "International Journal of Oral & Maxillofacial Implants" with 319 publications and "International Journal of Periodontics & Restorative Dentistry" with 273 publications. The ranking, publication counts, distribution according to Bradford's Law, and quartile values of the top 10 journals with the most publications are shown in Table 1.

Country Analysis

The United States had the highest publication and citation counts, followed by Italy, Germany, Japan, and China. The publication counts, citation counts, and centrality values according to collaboration analysis of the top 10 contributing countries are presented in Table 2.

Reference Analysis

The most cited article, with 731 citations, belonged to Buser et al[16]. The network formed by references aimed to evaluate the evidence-based separation of topic headings within the literature. Co-citation analysis revealed 912 nodes and 2,092 connections. The top 5 most cited and co-cited articles are summarized in Table 3. Cluster analysis based on co-citations divided the literature into 17 topic headings. The largest cluster was "titanium mesh exposure (Cluster #0)" with 110 articles. The clustering analysis map is shown in Figure 2.a, and the timeline view is displayed in Figure 2.b. The overall silhouette value of the clustering analysis was 0.8798, indicating a reasonable level of separation within the literature.

Keyword Analysis

Among 4,074 keywords, 422 keywords appeared at least 5 times. The network of these keywords is illustrated in Figure 3.a., and the graffiti representation of these keywords is depicted in Figure 3.b. When examining keywords associated with citation bursts visualized in Figure 3.c., the strongest citation burst was related to the keyword 'alveolar bone grafting,' which occurred between 2020 and 2023. The second most significant citation burst was associated with the keyword 'tissue engineering,' which occurred between 2010 and 2013.

Table 1. The metric properties of the top 10 journals with the most publications.

Rank	Journal Title	Number of Publications	Bradford Zone	Quarterly
1	Clinical Oral Implants Research	416	Zone 0	Q1
2	International Journal of Oral & Maxillofacial Implants	319	Zone 0	Q1
3	International Journal of Periodontics & Restorative Dentistry	273	Zone 0	Q2
4	Clinical Implant Dentıstry and Related Research	212	Zone 0	Q1
5	Journal of Periodontology	164	Zone 1	Q1
6	Journal of Oral and Maxillofacial Surgery	128	Zone 1	Q3
7	Journal of Oral Implantology	124	Zone 1	Q2
8	Implant Dentistry	120	Zone 1	Q2
9	International Journal of Oral and Maxillofacial Surgery	120	Zone 1	Q1
10	Journal of Clinical Periodontology	119	Zone 1	Q1

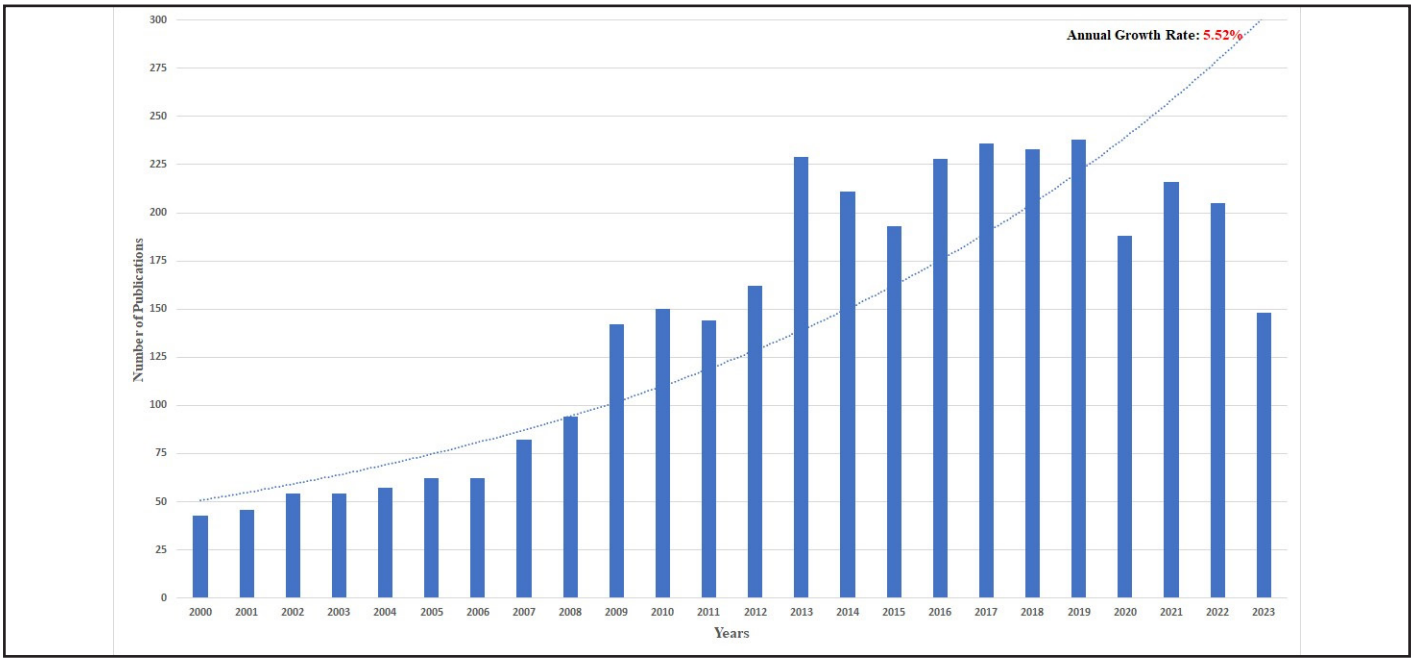

Figure 1. Number of publications by year and annual growth rate."

Table 2. Number of publications, number of citations, and centrality values of the top 10 countries with the most publications.

Country	Number of Publications	Number of Citations	Centrality Value
USA	612	15684	0.38
Italy	436	14829	0.14
Germany	345	6562	0.15
Japan	203	3821	0.09
China	180	1935	0.06
South Korea	162	2035	0.03
Brazil	160	2983	0.10
Spain	148	3291	0.11
Switzerland	146	6763	0.16
Israel	103	2832	0.02

Table 3. Top 5 articles with the highest metric values.

Top 5 Most Cited Articles		Top 5 Co-cited Articles	
Count	**References**	**Count**	**References**
731	Optimizing esthetics for implant restorations in the anterior maxilla: Anatomic and surgical considerations	76	Bone augmentation procedures in implant dentistry
629	A systematic review of the success of sinus floor elevation and survival of implants inserted in combination with sinus floor elevation - Part I: Lateral approach	70	Are there specific indications for the different alveolar bone augmentation procedures for implant placement? A systematic review
622	Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement?	62	Bone augmentation procedures in localized defects in the alveolar ridge: clinical results with different bone grafts and bone-substitute materials
506	Bone Augmentation Procedures in Implant Dentistry	61	Effectiveness of vertical ridge augmentation interventions: A systematic review and meta-analysis
491	Bone augmentation techniques	61	Effectiveness of lateral bone augmentation on the alveolar crest dimension: a systematic review and meta-analysis

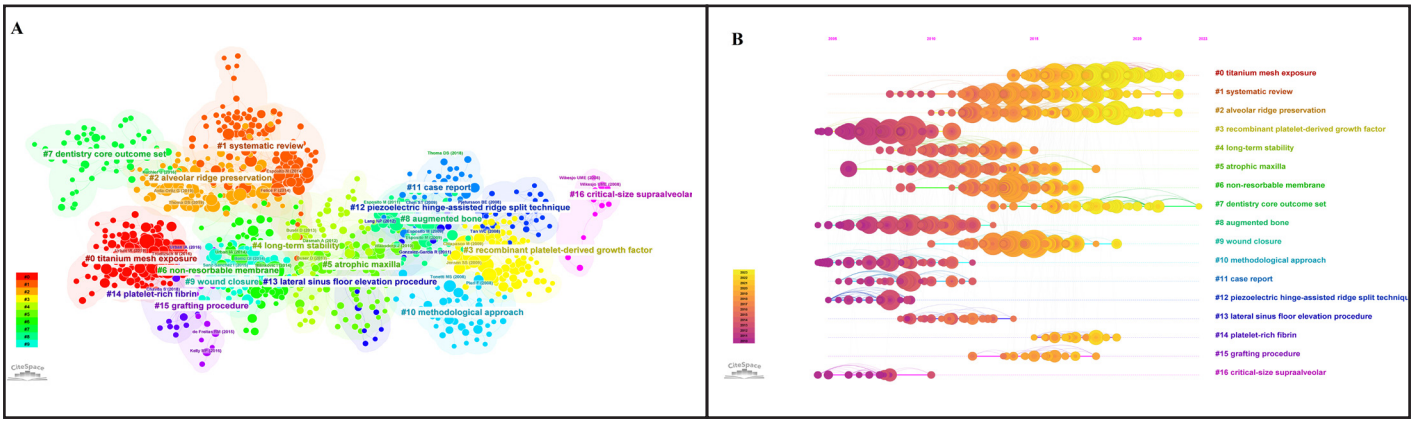

Figure 2. Co-citation analysis. A represents the Cluster analysis view, while B represents the Timeline view.

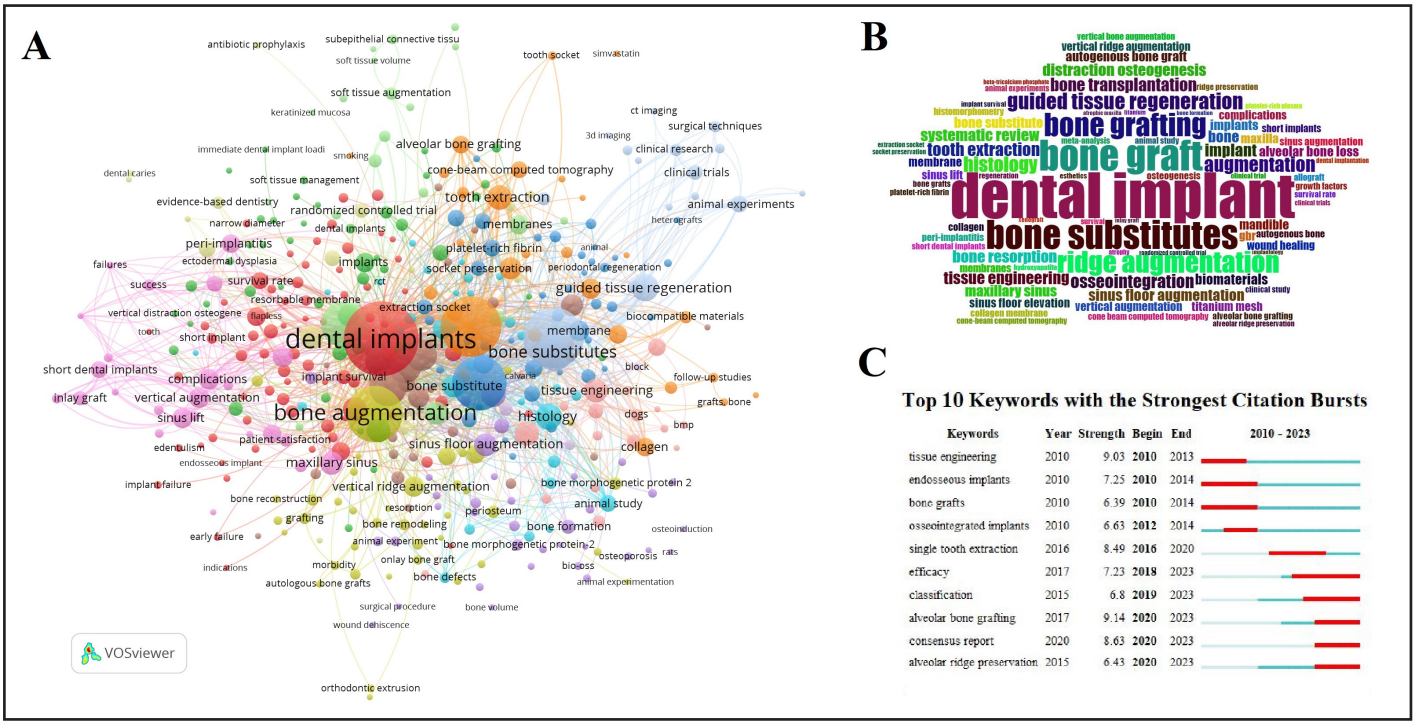

Figure 3. Keyword Analysis. A Co-occurrence network, B Graphite look and C Represents the top 10 keywords with the strongest citation brusts.

DISCUSSION

This study aims to present a bibliometric analysis of publications in the field of alveolar ridge augmentation, providing an overview of scientific production and development in this domain. Towards this purpose, publications related to Alveolar Ridge Augmentation from 2000 to 2023 were obtained from the Web of Science Core Collection, and they were analyzed using specially prepared programs for bibliometric analysis.

Bibliometric analysis aids in understanding trends and emphases within the literature, helping to identify priorities and potential research directions for the future [14, 17]. This article offers a panorama of academic effort and progress in the field of alveolar ridge augmentation. The obtained findings indicated that this field is a dynamic structure that is progressively growing, evolving, and diversifying into various topic areas.

Alveolar ridge augmentation is a commonly used procedure aimed at creating the appropriate bone volume required for dental implants or other restorative dental surgeries [18, 19]. Among the topics that have particularly garnered attention in current literature in this field are the selection of augmentation materials, the refinement of surgical techniques, and the long-term monitoring of outcomes [20, 21]. Factors such as the biocompatibility of augmentation materials, their impact on implant stability, and complication rates are especially important in the decision-making process for surgeons [22, 23]. Additionally, changes and advancements in surgical techniques have been a subject of discussion, particularly with the increasing use of minimally invasive approaches and digital Technologies [24]. Bibliometric analysis methods can be valuable in assessing new developments and clinical applications in the field of alveolar ridge augmentation. The results obtained through bibliometric analysis methods have the potential to provide more enlightening information for future research endeavors, aiming to enhance success rates of augmentation procedures and achieve better outcomes for patients.

The analysis results illustrate how the publication count in the field of alveolar ridge augmentation has changed over time and which topics have garnered more attention. Additionally, they reveal the countries and institutions leading in this area, as well as the authors contributing the most. Such data can provide insights into the formation of global collaborations and research networks in alveolar ridge augmentation. Identifying potential areas for future research is another important contribution of this study. The analysis results also highlight needs for further research in specific topics or methods and how these studies could impact the field. Furthermore, the results could provide hints on how multidisciplinary approaches or new technologies can be integrated into the realm of alveolar ridge augmentation.

Based on our findings, the United States had the highest publication and citation counts, and also the highest centrality value. This suggests that the United States is leading the efforts in this field and likely assisting other countries in finding new research topics. Additionally, countries like Japan, China, and South Korea had high publication counts but low centrality values, indicating that their studies had more localized impacts and were cited less by authors from other countries. To improve this situation, authors from countries with low centrality values are encouraged to engage in international collaborations and publish multi-national studies.

The most cited article belonged to Buser et al [16], and its main topic was to define key points to consider in dental implant treatment in the anterior maxilla. This study, published in 2004, has continued to remain relevant as the key points identified in this research are still applicable today. The second most cited article was a systematic review by Pjetursson et al [25], which examined sinus floor elevation using the lateral window approach. The study concluded that the procedure utilizing rough-surfaced implants covered by a membrane through the lateral window method achieved the highest success rate with a 98.3% implant survival rate three years later. Among the top 5 most cited articles, the other 3 articles did not focus on any specific topic but were related to bone augmentations.

Co-citation clustering analysis allowed us to identify evidence-based topics that the literature is divided into [10]. The more two different articles are co-cited, the more likely those publications are on the same topic. When performing co-citation clustering analysis, the frequencies of words used in the titles of these co-cited articles were evaluated to determine the cluster heading. Accordingly, the literature on alveolar ridge augmentation was divided into 17 subclusters. The largest and youngest cluster was Cluster #0, the 'titanium mesh exposure' cluster. The publications in this cluster were related to the use of titanium mesh in alveolar ridge augmentation. The recent decrease in the cost and increase in the popularity of titanium mesh is likely contributing to the rise in the number of publications. The significant advantages of titanium mesh, such as high biocompatibility, mechanical strength, flexibility, ease of shaping, promotion of cellular reactions, long-term durability, transparency, visibility, and minimal infection risk, have led to its increased use in alveolar ridge augmentation [26–30].

Certain topics have gained more importance over time, while others have lost significance. Notably, the use of PRF (platelet-rich fibrin) and alveolar crest split are among those that have decreased in importance. This decline could be due to other techniques proving more advantageous, and also the challenge of finding new aspects to explore regarding these two techniques.

Keywords play a crucial role in summarizing a paper's content and highlighting specific subjects or concepts [31, 32]. These keywords enable easier discovery of papers in databases or search engines [33]. Furthermore, topic selection is a critical component of papers, as focusing on a specific subject allows for in-depth knowledge production and expertise leadership

[32]. Keyword analysis can provide essential insights into the literature. The fact that 'Dental Implants' is the most frequent keyword indicates that alveolar ridge augmentation is strongly related to dental implants. Figure 3.c, which displays the changing popularity of keywords over time, is important for showing trends.

Limitations

This study had several limitations. First, the evaluated studies were limited to those published in English. Second, only a single database was utilized. The main issue here was the inability to combine data from multiple databases for analysis in Citespace. Consequently, only one database was used.

CONCLUSION

In conclusion, this study contributes to understanding the evolution and directions of academic efforts in the field of alveolar ridge augmentation. Researchers contemplating future work in this area can benefit from the insights provided by this analysis to identify potential areas of exploration and contribute to the advancement of the field. Monitoring significant developments and pioneering innovations should remain a primary objective for researchers in this domain, as they play a vital role in shaping the landscape and progress of the field.

Conflict of Interest: The author has no conflicts of interest to disclose.

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Ethical Statement: Ethical standards were adhered to in this study. Ethical approval was not required the bibliometric study.

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Original Research

Investigation of Cervical Posture, Sleep Quality and Perceived Health Risk in Technology Addicted Adolescents and Young Adults: A Comparative Study

Tuba Maden[1], Emir İbrahim Işık[2]

[1] Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Gaziantep, Turkey
[2] Department of Therapy and Rehabilitation, Abdi Sutcu Vocational School of Health Services, Cukurova University, Adana, Turkey

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Correspondence
Tuba Maden, PT, PhD
Address: Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Gaziantep, Turkey
E-mail: tuba.kmaden@gmail.com

ABSTRACT

Objective: The aim of this study was to compare the cervical posture, sleep quality, and perceived health risk of technology-addicted adolescents, young adults and their controls.

Methods: Adolescents and young-adults participants (n=160) were divided into four groups as addicted and non-addicted according to their age and Technology Addiction Scale scores. Cervical posture assessments were obtained by photographic analysis. Craniovertebral (CVA), craniohorizontal (CHA) and sagittal shoulder angle (SSA) values were recorded. Sleep quality was assessed with the Pittsburg Sleep Quality Scale. Participants' Perceived Health Risk was evaluated with a single-item, five-point Likert questionnaire.

Results: The addicted participants had worse CVA than both their controls (p=0.000). Participants' CHA and SSA angles were similar in addicted groups (p=0.710 and p=0.612, respectively). Addicted adolescents had worse sleep quality than addicted young-adults (p=0.005). Perceived Health Risk is low level in all groups and there were no significant differences (p=0.055).

Conclusion: Technology addiction affects the adolescent group more negatively than the young-adults. In the sample of adolescents and young-adults, individuals did not perceive excessive use of technological tools as a risk factor for their health. The degradation of CVA due to overuse of technological tools precedes the degradation of CHA and SSA. This can be explained by the fact that CVA is a more general angle that includes both the head-neck position and the vertebrae. It is necessary for public health and future health expenditures to educate and raise awareness of the more vulnerable adolescent group.

Keywords: Adolescent, Perception, Posture, Sleep quality, Technology Addiction

INTRODUCTION

Technology is a set of knowledge, including practical or technical information of a mechanical or industrial kind, which enables people to change natural conditions to make their lives more useful and enjoyable [1]. Due to technological developments, the use of technological devices such as smartphones, computers and tablets is becoming widespread among adolescents and young adults [2]. However, the level and form of technology use (excessive and inappropriate) can sometimes potentially damage physical and mental health, which can lead to social problems not only for the individual concerned, but also for their families and communities [3].

While new technologies provide people with an unlimited world, it is accepted that addiction to behaviors that seem harmless in certain situations has negative consequences [4]. Addiction is

not only a condition that develops depending on a substance. Technology addiction is also considered in the category of behavioral addictions. In DSM-5, addiction was removed from the framework of substance addiction and started to be evaluated more behaviorally with the concepts of withdrawal and tolerance [5]. Technology addiction is one of such behavioral addictions associated with overuse and uncontrolled use of technology. Technological addictions are part of non-toxic addictions and constitute addictive processes that develop through overuse and inappropriate use of what the internet offers, such as videos, video games and social networks [2, 6]. Technology addiction is characterized by salience, mood changes, tolerance (the need to use longer), depression and irritability when technology is not used, interpersonal conflicts and relapse [4, 7].

Adolescents and young adults are among the most affected groups despite being born in the digital age. For many people of this age group, technological approaches were used as an emotional pacifier as they were very effective in keeping children calm and quiet during childhood [8]. Gornicka et al. [9] states that spending more time in front of the screens of devices creates a highly sedentary lifestyle with a lack of physical activity, which leads to obesity and chronic diseases. As technology and its accessibility have become more widely available, the need to evaluate the effects of technology on people has also increased.

Technology addiction creates a risk for health by bringing mental, social, familial, academic, and physical problems [9]. Especially, there are studies showing that musculoskeletal problems and postural impairment frequently associates with and is related to technology addiction [10]. When the variables predicting addiction are considered, sleep quality is also an important variable [11]. At this point, the relationship between technology addiction, posture, sleep quality and perceived health risk is important in determining risk groups, risk factors and appropriate preventive treatment approaches. It is stated that individuals who are addicted to technology have impaired cervical posture, headaches or sleep problems [12, 13]. However, in these studies, individuals from different age groups were not investigated or the age of first meet with technology and exposure was ignored. It is not known how much posture or sleep quality is affected by the exposure of participants from different age groups to the same technological factors. Therefore, in this study, cervical posture, sleep quality and perceived health risk in technology-addicted adolescents, young adults and their controls will be compared.

Main Points;

- The CVA values of the addicted groups were worse than the non-addicted groups.
- The adolescent group in sleep quality was worse affected by excessive use of technological devices than younger adults,
- One of the cervical posture parameters, CVA is more general as it includes both head and neck and vertebrae, so it may be affected first order according to CHA and SSA.
- All participants in our sample had low and similar level awareness of the negative health effects of excessive use of technological tools.
- Raising awareness about technology addiction is very important in terms of public health and future health expenditures.

MATERIALS AND METHODS

This cross-sectional and non-interventional study was conducted on adolescents and young adults. Ethical approval was obtained from the ethical committee of Çukurova University (Ethics committee decision No: 2023/72 and Date: 04.02.2023). The participants were informed about the purpose and content of the study. Informed consent has been obtained from all participants included in the study.

The inclusion criteria were (a) volunteering to participate in this research, (b) having fluent Turkish speaking skill, (c) having sufficient communication skills without adequate hearing and speech problems. The exclusion criteria were (a) having drug use that may affect sleep duration, (b) having a history of trauma or pathology in the neck region that may affect posture, (c) having chronic or metabolic disease. The flow-chart diagram is given in Figure 1.

Population and Randomization: The research population consisted of 627 participants studying in a high school and a vocational school, and the sample consisted of 160 participants who voluntarily wanted to participate in the research. In order to determine the group of participants who matched the criteria for inclusion in the sample, they were randomly distributed to four groups with a computer program (https://www.randomizer.org/) without repeating the numbers from 1-160; 40 technology-addicted adolescents, 40 technology-addicted young adults, 40 non-technology addicted adolescents and 40 non-technology addicted young adults. The assessments were performed at the same time of the day to eliminate the effect of fatigue.

The data of the study were collected through the following forms and tools.

Demographic Form: Demographic data of the subjects were recorded on a form. The form included the age, gender, the year of meeting with the internet, duration of internet usage.

Technology Addiction Scale: This scale consists of 24 items and 4 sub-dimensions of 6 items each (using social networking, instant messaging, playing online games and using websites). It is aimed to determine the level of technology addiction on the scale prepared in a five-point Likert format. The scale is rated as 1 "never", 2 "rarely", 3 "medium frequency", 4 "very often", 5 "always". In the evaluation of the scale, the total score is obtained by summing the answers given to the items. The maximum score of the scale is 120 and the minimum score is 24. A higher score means higher technology addiction. A score of 50 and above indicates moderate dependency. Individuals were divided into dependent and non-dependent groups based on the cut-off point of the scale [14].

Cervical Posture: Cervical posture assessments were obtained by photogrammetry technique. Photogrammetry shows good validity for the analysis of cervical posture [15]. The digital camera was placed on a fixed surface at a distance of 1.5 meters. While the participant was in a standing position, the height of the digital camera was adjusted so that it was at the shoulder level of the participant. A marker was placed on the spinous process of C7 and photographs were taken from the left side of each individual. In order to ensure the correct posture of the participants, photographs were taken while looking at a fixed point in front of them. The craniovertebral angle (CVA), craniohorizontal angle (CHA) and sagittal shoulder angle (SSA) were determined on the photographs taken in the standard position [16].

Craniovertebral Angle: Craniovertebral angle value was used to determine the head posture. Craniovertebral angle (CVA) is the angle of the line connecting the midpoint of the ear tragus with the spinous process of the C7 with the horizontal line. CVA measurement is one of the most common angles used to assess anterior head posture and is a good indicator for anterior head posture, and its reliability and validity have been confirmed in previous studies [15]. CVA angle value 53.1°- 56.8° indicates normal head posture [15].

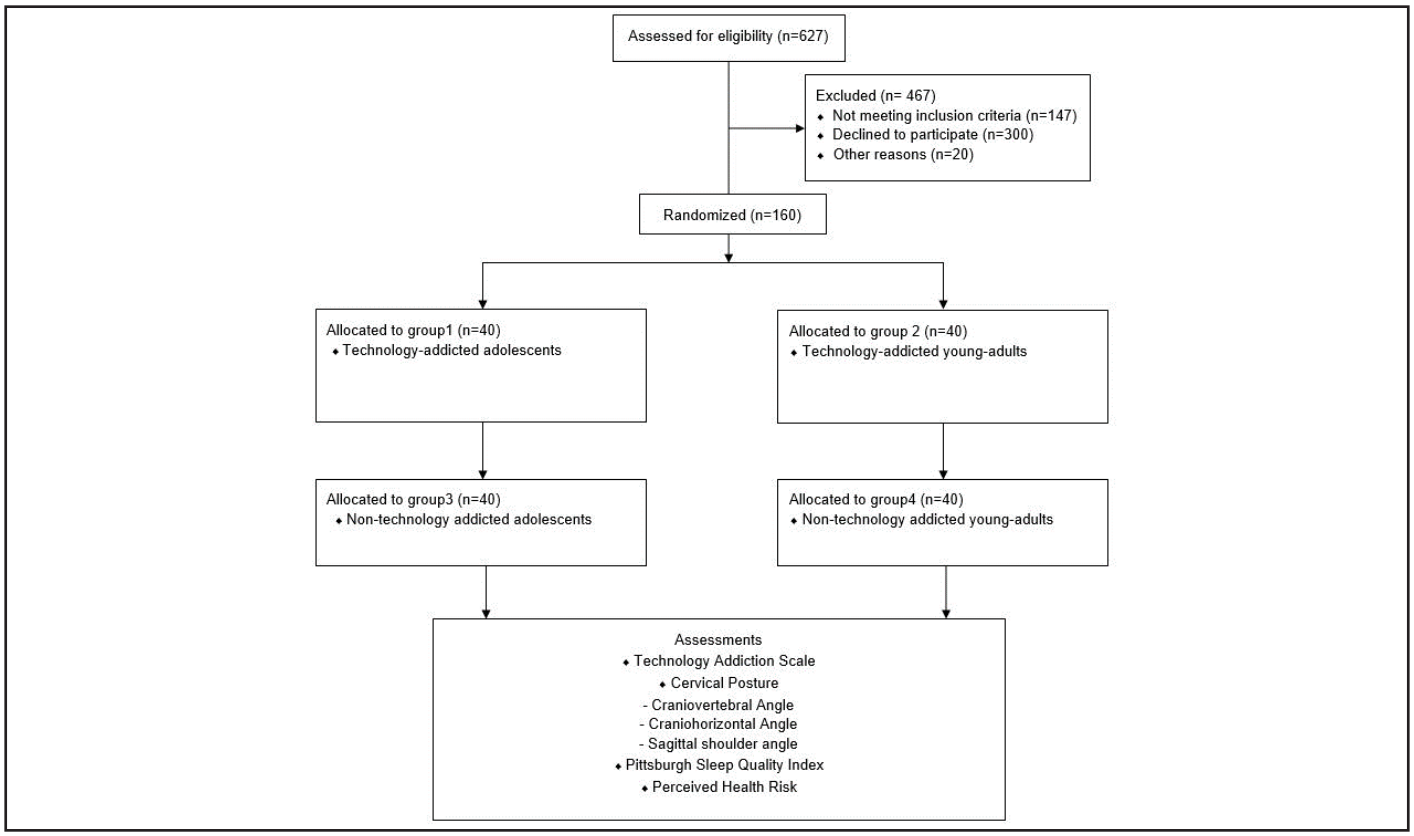

Figure 1. Flow-chart diagram

Craniohorizontal Angle: A horizontal line is drawn across the ear tragus to determine the craniohorizontal angle. Another horizontal line is drawn, starting from the lateral canthus of the eye and joining the tragus of the ear. The intersection of these two lines forms the craniohorizontal angle. This angle gives information about the position of the head and upper cervical spine relative to each other [17].

Sagittal Shoulder Angle: To determine this angle, a horizontal line is drawn through C7. This line is joined by another line joining the midpoint of the greater tuberculum of the humerus and the posterior aspect of the acromion. The angle of intersection of the two lines is the sagittal shoulder angle. This angle allows the forward shoulder position to be measured. A reduction in sagittal shoulder angle means that the shoulder is more anterior than C7. This results in a more rounded shoulder look [17].

Pittsburgh Sleep Quality Index (PSQI): PSQI is a 19-item scale that reports sleep quality and sleep disturbance in the last month with self-report. It consists of a total of 24 questions. 19 of these questions are answered by the person, and the remaining 5 questions are to be answered by the person's spouse or roommate, if any. The scale has 18 questions included in the scoring. These questions consist of 7 sub-components. Subcomponents are evaluated in the range of 0-3 points. The sum of the scores of the seven subcomponents gives the score of the index. The minimum score on the index is 0, and the maximum score is 21. A score of 5 or higher indicates poor sleep quality. It is valid and reliable in children and adolescents [18, 19].

Perceived Health Risk: Perceived health risk assessment will be evaluated with a five-point Likert type (1-strongly agree, 2-agree, 3-neither agree or disagree, 4-disagree, 5-strongly disagree). Participants will be asked to answer how true the question "technology addiction is a threat to my health" is for themselves [20].

Statistical Analysis

The Statistical Package for the Social Sciences version 22.0 software was used for statistical analysis. The frequency in percentage (%) and mean±standard deviation (X ± SD) of the study variables were presented. The normality of distribution was tested with the Kolmogorov-Smirnov test. Independent-t test was used to compare the parametric data among the groups. The statistical significance level was set at $p < 0.05$. G*Power application was used for post-hoc power analysis. The post-hoc power analysis was calculated %80 with one-tail, 0.05 Type I error, and effect size 0.56 in accordance with PUKİ.

RESULTS

The information of participants is shown in Table 1. The number of females in groups was higher than males, but not non-addicted young adults. The age of meeting the internet for the participants in the addicted group was younger than the other groups. The daily internet usage time was higher in the dependent adolescent group than in the other groups (Table 1).

When the CVA values in addicted and non-addicted groups were compared, there was a statistically significant difference (Table 2). The CVA of addicted adolescents and addicted young adults were similar (p=0.326). Participants' CHA and SSA angles were similar in addicted groups (p=0.710 and p=0.612, respectively) (Table 2). A significant difference was determined between adolescents and young adults in addicted participants' sleep quality (p=0.005) (Table 2). Perceived Health Risk is low level in all groups and there were no significant differences according to addiction (p=0.055) (Table 2).

Table 1. Characteristics and internet usage information of all participants

Variables	Addicted Adolescents	Non- Addicted Adolescents	Addicted Young Adults	Non-Addicted Young Adults
Age (years)	15.44±2.27	15.85±2.53	20.22±2.67	20.48±2.67
Gender (f/m) **%**	22/18 55/45	22/18 55/45	24/16 60/40	16/24 60/40
Technology Addiction Scale (Score)	66.72±18.28	44.70±13.84	55.37±18.07	41.77±15.60
Age of first Internet use (year)	9.62±2.73	10.89±2.63	11.95±2.28	12.50±3.28
Duration of Internet Usage (daily) (hours)	4.17±0.98	3.40±1.19	3.45±1.15	3.10±1.21

f: female, m: male.

Table 2. Distribution of cervical posture, sleep quality, and perceived health risk data according to group

Variable	Addicted Adolescents	Non- Addicted Adolescents	p^1	Addicted Young Adults	Non-Addicted Young Adults	p^2	p^3
Cervical Posture (°)							
CVA	67.97±5.09	48.85±5.95	0.000*	66.97±3.48	46.69±5.07	0.000*	0.326
CHA	21.55±15.29	17.00±12.39	0.159	22.87±15.20	22.20±11.98	0.843	0.710
SSA	54.69±20.47	48.08±18.61	0.146	52.45±18.63	48.80±18.79	0.386	0.612
Pittsburg Sleep Quality Index (Score)	8.62±3.69	6.75±2.88	0.013*	6.37±3.28	6.95±3.03	0.419	0.005*
Perceived Health Risk (Score)	2.52±0.93	2.20±1.15	0.171	2.10±0.99	2.30±1.28	0.448	0.055

*$p<0.05$ is statistically significant, independent t-test, p^1: Comparison of adolescents, p^2: Comparison of young adults, p^3: Comparison of addicted groups, CVA: Cranio-Vertebral Angle, CHA: Cranio-Horizontal Angle, SSA: Sagital Shoulder Angle

DISCUSSION

The aim of this study was to compare the cervical posture, sleep quality, and perceived health risk of technology-addicted adolescents, young adults and their controls. The study shown that participant tech-addicted individuals had worse CVA and sleep quality than both their controls. While the posture effects of individuals in different age groups were similar, the sleep quality of addicted adolescents was worse than that of addicted adults. This shows us that meeting technology at an early age and being exposed to mass media in different positions impair the health of individuals in the adolescent group. Adolescent and young adult groups did not perceive this exposure as a health risk due to the fact that the developing technology is everywhere in our lives and is easily accessible. Our study is unique in terms of comparing addicted and non-addicted individuals in different age groups.

The use of the internet and technological devices is inevitable today and it affects individuals of all ages in society at different levels. Factors such as the widespread use of mass media such as tablets, televisions, smart phones and easy access to the internet trigger technology addiction. There are many studies in the literature investigating the negative effects of technology addiction in young individuals. The main ones of these effects can be listed as psychological factors, sleep disorders and posture disorders [21]. In particular, there are studies examining the relationship between smartphone addiction and cervical posture. In these studies, posture-related scales were generally used [21]. It has been shown that craniocervical posture is adversely affected by excessive, uncontrolled and damaging use of the smartphone [22]. It has been emphasized that temporomandibular joint pathologies may also develop due to the effect on the craniovertebral angle [23]. In a study by Cetin et al., the relationship between smartphone use and cervical posture was investigated, and a strong relationship was found only between CVA and addiction [24]. The posture parameters we used in our study were compared for the cervical posture of individuals addicted and non-addicted smartphones in the young-adults population, and a significant difference was found only in CVA [25]. In our study, only the CVA was found to be significantly impaired in the posture analyzes of the addicted groups, consistent with the literature. We think that the fact that the CVA is similar in the addicted adolescents and addicted young adults can be explained by exposure similarity. In addition, another study compared postural changes after 5 minutes of mobile phone use and showed an increase in shoulder protraction on the non-dominant side, kyphosis, neck lateral flexion, and pelvic obliqueness. In other words, it has been discussed that postural deteriorations are not limited to the cervical region, but may spread throughout the body in the future [26]. Based on this view made specifically for the smartphone, although the technology-addicted individuals included in our sample frequently and especially use the phone, we think that the influence does not affect the shoulder position, since technology addiction includes different positions such as tablet and television. In addition, not knowing the sitting times or physical activity levels of the participants is one of the limitations of our study.

Excessive use of technology negatively affects sleep quality in adolescents and young adults. Anxiety and loneliness, which increase with the use of the Internet or technological tools, are an indicator of psychological problems in the same population, and the presence of psychological problems is also associated with sleep problems. In a study conducted by Coskun et al., it was stated that students often browse the computer or the Internet

and watch television before falling to sleep [27]. Exposure to blue light with technological tools reduces the release of melatonin, which plays an important role in sleep quality [28]. This causes difficulty in falling asleep, disruption of sleep rhythm and poor sleep quality [27]. When the sleep quality of young people addicted and non-addicted internet was compared, addiction and sleep quality were negatively correlated. [29, 30]. In another study investigating the causes of sleep problems in the adolescent group, it was emphasized that technology use was at the forefront [31]. Besides, it was shown that poor sleep quality is associated with a deterioration of posture [32]. In our study, sleep quality was worse in the addicted groups and sleep quality was affected more in the adolescent group than in the other groups. We are of the opinion that the sleep rhythm and quality can normalize over time by adapting the body to the use of technological tools at a young age. There is a need for longitudinal studies in which technology-addicted individuals are followed from a young age.

Although the negative effects of technological tools on health are known, it is important how much risk users perceive this factor. Because being aware of the negative effects of technology addiction will prevent adverse consequences. Technological tools have important effects on mental and psychological health and can change the daily activity routines of adolescents and children, especially in the most vulnerable group [33]. However, how this danger is perceived by users is even more important. Perceived disorders related to the use of digital technology in adolescents between the ages of 10-15 were investigated and 91% of adolescents reported that they had problems in their real lives due to the virtual environment [34]. In the study conducted by Buda et al., it was shown that the use of social media caused two times less sleep quality and life satisfaction in the child and adolescent group [35]. Individuals in our sample had low levels of awareness, regardless of their addiction level. It would be beneficial to provide trainings on the negative effects of excessive use of technological tools on health, especially for groups such as children and adolescents who are vulnerable.

According to the findings of the study, adolescents are more affected by technology addiction than young adults. Addicted adolescents have worse CVA and sleep quality than non-addicted adolescents. CHA and SSA were similar in groups. It may be due to the fact that the CVA angle, which leads to postural changes, is a more general parameter since it covers both the head-neck and the trunk. In addition, since the concept of technology addiction is not limited to smartphone use, CHA and SSA exposure may be less in tablet and computer use. In our study, it was determined that the groups did not perceive technology use as a risk factor that could negatively affect health. Providing trainings that include the negative effects of excessive use of technological tools on health will prevent health expenditures in the future, especially in order to increase the awareness of adolescents.

Limitations

This study has a number of limitations. Firstly, the physical activity or sports habits of the participants are unknown. Second, sitting time and sitting position, which are other factors that may affect the head-neck posture of individuals, were not recorded. Thirdly, since the data of our study were collected from a single center, the sample population representation is limited.

CONCLUSIONS

It has been shown that technology addiction affects the adolescent group more negatively than the young-adults. In the sample of adolescents and young-adults, individuals did not perceive excessive use of technological tools as a risk factor for their health. The degradation of CVA due to the overuse of technological tools precedes the degradation of CHA and SSA. This can be explained by the fact that CVA is a more general angle that includes both the head-neck position and the vertebrae. Considering the negative effects of technological tools and the low awareness levels of the participants, it is necessary for public health to educate and raise awareness of the more vulnerable adolescent group. Actions such as trainings and informative brochures on topics such as head and neck posture, sleep quality and hygiene will prevent future health expenditures.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Informed Consent: The participants were informed about the purpose and content of the study. Informed consent has been obtained from all participants included in the study.

Ethical Approval: Ethical approval was obtained from the ethical committee of Cukurova University (ethics committee decision No: 2023/72).

Author Contributions: Conception: TM - Design: TM - Supervision: TM - Fundings: x -Materials: TM, EİI- Data

Collection and/or Processing: EİI- Analysis and/or Interpretation: TM, EİI - Literature: TM, EİI - Review: TM, EİI - Writing: TM, EİI - Critical Review: TM, EİI

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Original Research

Analysis of the 50 Most Cited Articles on Dabigatran: A Bibliometric Study

Sedat Yasin[1], Erman Altunisik[2]

[1] Department of Neurology, Gaziantep University Faculty of Medicine, Gaziantep, Turkey
[2] Department of Neurology, Adiyaman University Faculty of Medicine, Adiyaman, Turkey

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Correspondence
Sedat Yasin
Address: Department of Neurology, Gaziantep University Faculty of Medicine, Gaziantep, Turkey.
E mail: drsedatyasin@hotmail.com

ABSTRACT

Objective: Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults. Anticoagulation significantly reduces stroke and related mortality in AF patients. This study conducted a bibliometric analysis of the top 50 most-cited articles in the literature on dabigatran, the first new-generation oral anticoagulant.

Methods: We searched the Web of Science for articles with dabigatran in the title. The top 50 most cited articles (T50) were selected. Characteristics of the articles (such as author, source, institution, country, scientific category, number of citations, citation density, and citations per article) were analyzed.

Results: T50 had a total of 33,301 citations. The average number of citations per article was 666. The United States of America (USA) was the most prolific country in T50, with 36 papers and 26,043 citations. Wallentin Lars from Uppsala University was the most prolific author, with 14 articles and 13,532 citations. *Circulation* was the most prolific journal, with 11 articles.

Conclusions: We analyzed the classic publications on dabigatran, the first new-generation oral anticoagulant. The most prolific country was the USA, author was Wallentin, and journal was *Circulation*. Researchers and clinicians can easily access influential publications by reviewing our study.

Keywords: Bibliometrics, dabigatran, Web of Science, citation, stroke.

INTRODUCTION

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by irregular atrial activation. It is the most common cardiac rhythm disorder in the adult population and occurs more frequently with increasing age. It is easily detected by non-invasive methods. AF is an important cause of morbidity and mortality due to the increased risk of systemic embolism and stroke [1,2]. AF increases the risk of ischemic stroke by 3 to 5 times and is estimated to be responsible for 15% of all strokes worldwide [3]. Stroke in AF patients has been associated with longer hospitalization, greater disability, larger infarct volume, higher mortality in the first 30 days, and less discharge [4].

Anticoagulant therapy significantly reduces stroke and related mortality in AF patients [5]. Oral anticoagulation was the only option with vitamin K antagonists (warfarin) until recently. The risk of intracranial hemorrhage is 7-10-fold higher in warfarin-treated patients (INR 2.5-4.5), and mortality is around 60% [6]. While warfarin has been the primary anticoagulant drug for preventing systemic embolism and stroke in AF, new-generation

oral anticoagulants (NOAC) have recently entered clinical use. NOACs are preferable to warfarin because of their more rapid onset and cessation of action, fewer drug or food interactions, and no need for frequent laboratory monitoring at fixed doses [7]. The Randomized Evaluation of Long-term Anticoagulation Therapy (RELY) trial found that NOACs prevented stroke in patients with AF. Dabigatran was the first NOAC to receive clinical approval for this indication [8]. Dabigatran etexilate is an oral prodrug. It is converted by a serum esterase into dabigatran, a reversible direct thrombin inhibitor. [9].

Bibliometrics is an interdisciplinary method based on quantitative analysis of scientific literature using mathematical and statistical tools [10]. Assessing the research trends and impact of published literature in a particular field can provide valuable data to researchers planning a new research topic. It may be difficult to focus on a specific topic and find effective publications within many published journals and articles. Bibliometric analysis is a useful tool to overcome these problems because it provides a cross-sectional view of existing studies on the topic of interest [11]. Bibliometrics also describes the impact factor (IF) of journals in which manuscripts appear; IF analyzes the impact of a manuscript on the scientific community based on the number of manuscripts that cite it [12]. A review of frequently cited articles can provide information about the dominant areas of a discipline and indicate trends and growth in specific fields [13].

In this study, we aimed to comprehensively analyze the current state of the subject through a bibliometric analysis of the 50 most cited articles on dabigatran.

MATERIALS AND METHODS

Articles with "dabigatran" in the title were searched in Web of Science (WoS). Editorials, book chapters, and abstracts were excluded. Only original articles and reviews were analyzed. We excluded publications that were not in the Science Citation Index-Expanded (SCI-E) category according to WoS indexing and those written in languages other than English.

Articles were ranked by prioritizing the highest number of citations. The first 50 articles in the ranking were selected (T50). The characteristics of the publications (such as country, institution, author, source, scientific category, number of citations, number of citations per article, and citation density) were analyzed. Full text of each publication in the list were independently screened by two authors (EA, SY). In case of disagreement, the opinion of the senior author (EA) was used. Many publications that included the name of the drug in the abstract or full text were irrelevant to the study; thus, the study was limited to publications that included the name of the drug in the title. The results of the analysis were presented as quantitative and descriptive data. No statistical significance test was used.

The analysis occurred between August 08-10, 2023. This and similar studies are exempt from ethical approval because the data used are publicly available and no human or animal data are used [11]. The authors of this study are not affiliated with the company or organization to which the drug subject of the study is affiliated. The data obtained from the WoS database was uploaded to VOSviewer software. Web mapping showing the interaction and density of publications was made with VOSviewer software. VOSviewer is free software for bibliometric analysis, available at https://www.vosviewer.com [14].

Main Points;

- The most cited publications on dabigatran have fluctuated over the years. The number of citations of the most cited studies varies between 251 and 7907, and thus all of them can be considered as "classics" in their field.
- USA was the most productive country in the top 50 most cited articles.
- The citation explosion on dabigatran was driven by the study clinical trial that paved the way for its approval for clinical use.

RESULTS

A total of 3,397 publications were found in the WoS database for publications with the term "dabigatran" in the title. After excluding publications whose language was not English and indexed outside the SCI-E category according to WoS indexing, 3,038 publications were obtained. Including only original articles and reviews, 1,370 publications remained. Among these publications, the 50 most cited articles were selected and analyzed.

The number of publications and citations in T50 by year is shown in Figure 1. Publications and citations within T50 fluctuated according to year. The most publications were published in 2011 (n=10). The highest number of citations in a year was 3,426 in 2013.

The H index for T50 was 50. The publications had a combined total of 33,301 citations. The average number of citations per article was 666. 'Dabigatran versus Warfarin in Patients with Atrial Fibrillation' was the most cited paper (total citations: 7,907) and had the highest average annual citation rate (annual citations: 527). Data for T50 are presented in Table 1.

Data on the five most influential countries in the T50 are shown in Table 2. The United States of America (USA) was the most productive country, with 36 articles, 723 citations on average per article, 26,043 combined citations, and an annual citation average of 1,371. The network map showing the interaction between these countries is shown in Figure 2.

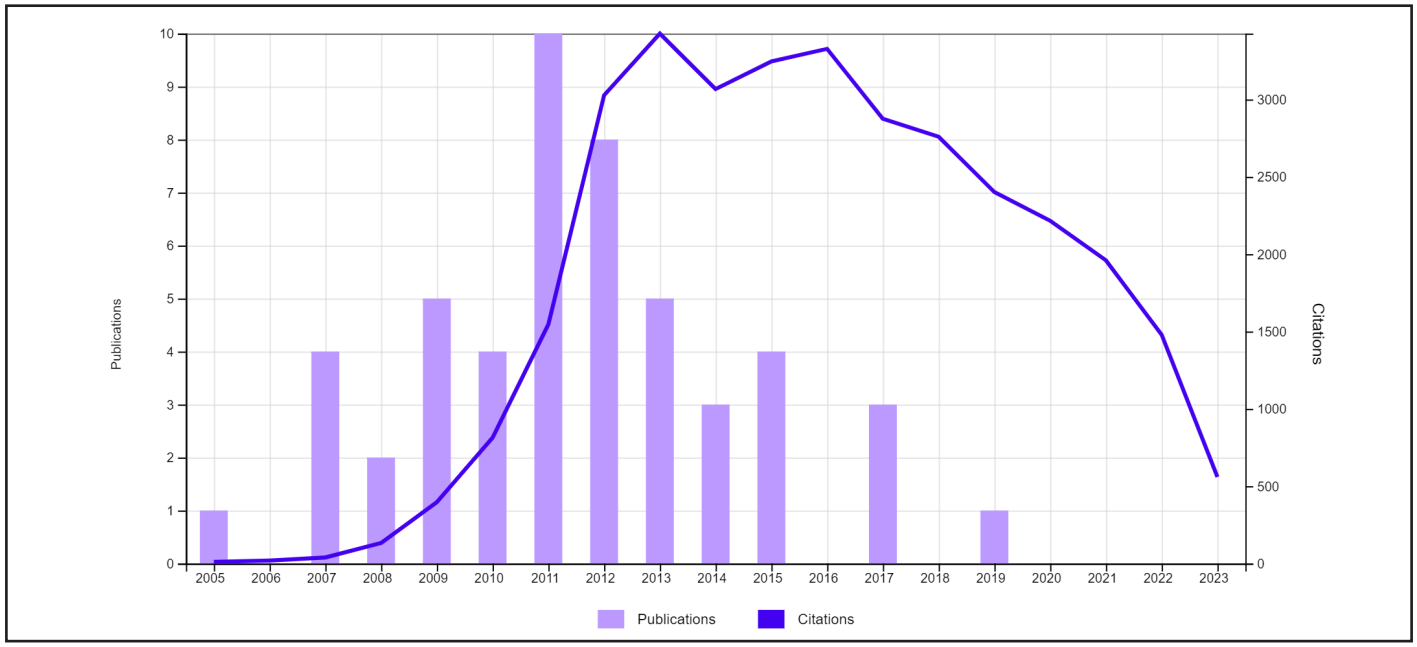

Figure 1. Graph of the number of publications and citations over years

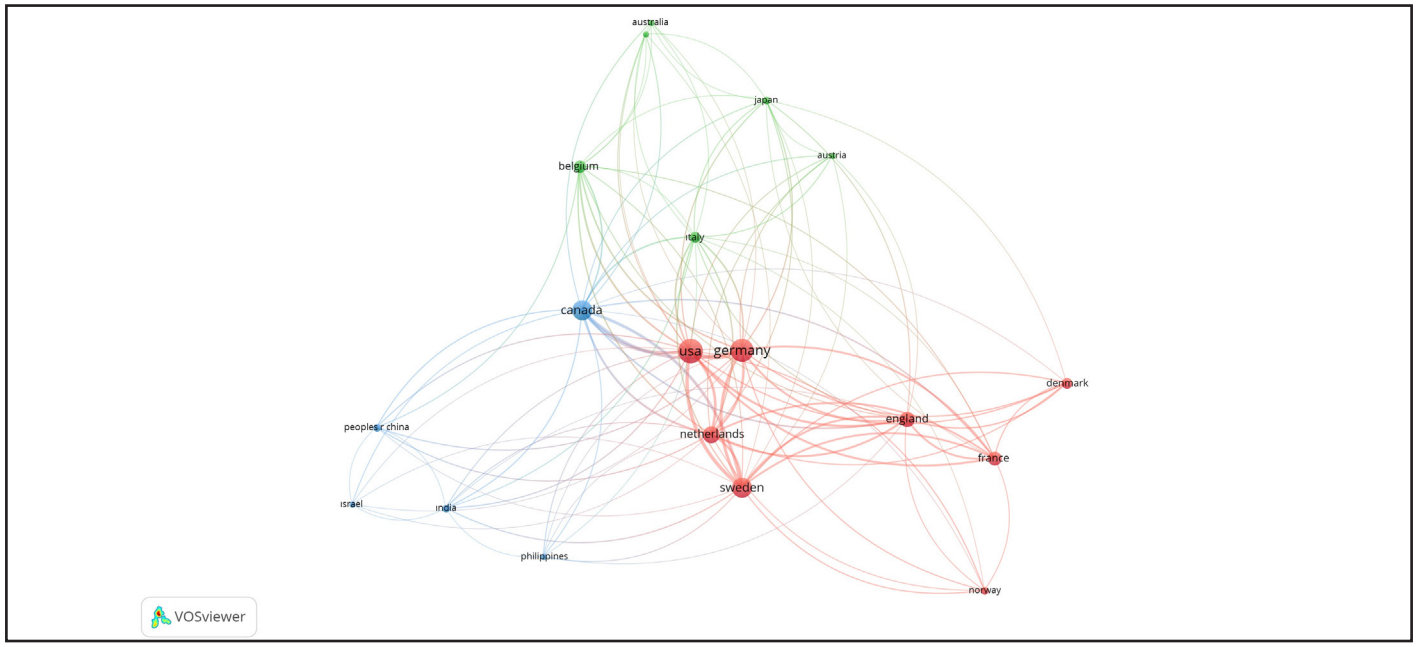

Figure 2. Network visualization map of country co-authorship

Table 1. Data for T50

	Article Title	Journal	Publication Year	DOI	Total Citations	Average per Year
1	Dabigatran versus Warfarin in Patients with Atrial Fibrillation.	NEW ENGLAND JOURNAL OF MEDICINE	2009	10.1056/NEJMoa0905561	7907	527,13
2	Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism.	NEW ENGLAND JOURNAL OF MEDICINE	2009	10.1056/NEJMoa0906598	1841	122,73
3	Dabigatran etexilate - a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity	THROMBOSIS AND HAEMOSTASIS	2010	10.1160/TH09-11-0758	1082	77,29
4	Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects	CIRCULATION	2011	10.1161/CIRCULATIONAHA.111.029017	1071	82,38
5	Dabigatran versus Warfarin in Patients with Mechanical Heart Valves	NEW ENGLAND JOURNAL OF MEDICINE	2013	10.1056/NEJMoa1300615	924	84
6	Idarucizumab for Dabigatran Reversal	NEW ENGLAND JOURNAL OF MEDICINE	2015	10.1056/NEJMoa1502000	898	99,78
7	Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation	NEW ENGLAND JOURNAL OF MEDICINE	2017	10.1056/NEJMoa1708454	863	123,29
8	Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial	LANCET	2007	10.1016/S0140-6736(07)61445-7	862	50,71
9	Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial	CIRCULATION	2011	10.1161/CIRCULATIONAHA.110.004747	859	66,08
10	Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial	LANCET	2010	10.1016/S0140-6736(10)61194-4	786	56,14
11	Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial	JOURNAL OF THROMBOSIS AND HAEMOSTASIS	2007	10.1111/j.1538-7836.2007.02748.x	760	44,71
12	The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects	BRITISH JOURNAL OF CLINICAL PHARMACOLOGY	2007	10.1111/j.1365-2125.2007.02899.x	716	42,12

13	Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism	NEW ENGLAND JOURNAL OF MEDICINE	2013	10.1056/NEJMoa1113697	709	64,45
14	Treatment of Acute Venous Thromboembolism With Dabigatran or Warfarin and Pooled Analysis	CIRCULATION	2014	10.1161/CIRCULATIONAHA.113.004450	651	65,1
15	The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	2014	10.1016/j.jacc.2013.07.104	645	64,5
16	Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate	CLINICAL PHARMACOKINETICS	2008	10.2165/00003088-200847050-00001	645	40,31
17	Idarucizumab for Dabigatran Reversal - Full Cohort Analysis	NEW ENGLAND JOURNAL OF MEDICINE	2017	10.1056/NEJMoa1707278	615	87,86
18	Influence of Renal Impairment on the Pharmacokinetics and Pharmacodynamics of Oral Dabigatran Etexilate An Open-Label, Parallel-Group, Single-Centre Study	CLINICAL PHARMACOKINETICS	2010	10.2165/11318170-000000000-00000	572	40,86
19	The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans	DRUG METABOLISM AND DISPOSITION	2008	10.1124/dmd.107.019083	546	34,13
20	Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation	CIRCULATION	2015	10.1161/CIRCULATIONAHA.114.012061	526	58,44
21	Oral Thrombin Inhibitor Dabigatran Etexilate vs North American Enoxaparin Regimen for Prevention of Venous Thromboembolism After Knee Arthroplasty Surgery	JOURNAL OF ARTHROPLASTY	2009	10.1016/j.arth.2008.01.132	487	32,47
22	A specific antidote for dabigatran: functional and structural characterization	BLOOD	2013	10.1182/blood-2012-11-468207	448	40,73
23	Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial	CIRCULATION	2012	10.1161/CIRCULATIONAHA.111.090464	424	35,33
24	Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial	EUROPEAN HEART JOURNAL	2011	10.1093/eurheartj/ehr113	416	32
25	Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban	THROMBOSIS AND HAEMOSTASIS	2012	10.1160/TH12-03-0179	415	34,58

26	Dabigatran Versus Warfarin in Patients With Atrial Fibrillation An Analysis of Patients Undergoing Cardioversion	CIRCULATION	2011	10.1161/CIRCULATIONAHA.110.977546	414	31,85
27	Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source	NEW ENGLAND JOURNAL OF MEDICINE	2019	10.1056/NEJMoa1813959	402	80,4
28	Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial	CIRCULATION	2013	10.1161/CIRCULATIONAHA.112.115386	373	33,91
29	Dabigatran with or without concomitant Aspirin compared with Warfarin alone in patients with nonvalvular atrial fibrillation (PETRO study)	AMERICAN JOURNAL OF CARDIOLOGY	2007	10.1016/j.amjcard.2007.06.034	366	21,53
30	Efficacy and Safety of Dabigatran Etexilate and Warfarin in Real-World Patients With Atrial Fibrillation A Prospective Nationwide Cohort Study	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	2013	10.1016/j.jacc.2013.03.020	353	32,09
31	Dabigatran Association With Higher Risk of Acute Coronary Events Meta-analysis of Noninferiority Randomized Controlled Trials	ARCHIVES OF INTERNAL MEDICINE	2012	10.1001/archinternmed.2011.1666	343	28,58
32	A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial	JOURNAL OF THROMBOSIS AND HAEMOSTASIS	2005	10.1111/j.1538-7836.2004.01100.x	332	17,47
33	Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Atrial Fibrillation	ANNALS OF INTERNAL MEDICINE	2011	10.7326/0003-4819-154-1-201101040-00289	327	25,15
34	Intracranial Hemorrhage in Atrial Fibrillation Patients During Anticoagulation With Warfarin or Dabigatran The RE-LY Trial	STROKE	2012	10.1161/STROKEAHA.112.650614	326	27,17
35	Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial	LANCET NEUROLOGY	2010	10.1016/S1474-4422(10)70274-X	321	22,93
36	Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) Versus Warfarin in Patients With Atrial Fibrillation	AMERICAN JOURNAL OF CARDIOLOGY	2012	10.1016/j.amjcard.2012.03.049	319	26,58
37	Efficacy and Safety of Dabigatran Compared With Warfarin in Relation to Baseline Renal Function in Patients With Atrial Fibrillation A RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) Trial Analysis	CIRCULATION	2014	10.1161/CIRCULATIONAHA.113.003628	306	30,6

38	Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II) A randomised, double-blind, non-inferiority trial	THROMBOSIS AND HAEMOSTASIS	2011	10.1160/TH10-10-0679	303	23,31
39	Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial	CIRCULATION	2012	10.1161/CIRCULATIONAHA.111.055970	290	24,17
40	Impact of dabigatran on a large panel of routine or specific coagulation assays Laboratory recommendations for monitoring of dabigatran etexilate	THROMBOSIS AND HAEMOSTASIS	2012	10.1160/TH11-11-0804	280	23,33
41	Hemostatic Therapy in Experimental Intracerebral Hemorrhage Associated With the Direct Thrombin Inhibitor Dabigatran	STROKE	2011	10.1161/STROKEAHA.111.624650	269	20,69
42	Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation	NEW ENGLAND JOURNAL OF MEDICINE	2017	10.1056/NEJMoa1701005	266	38
43	Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study	THROMBOSIS AND HAEMOSTASIS	2012	10.1160/TH11-11-0784	264	22
44	Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran	AMERICAN HEART JOURNAL	2009	10.1016/j.ahj.2009.02.005	263	17,53
45	Pharmacology, Pharmacokinetics, and Pharmacodynamics of Dabigatran Etexilate, an Oral Direct Thrombin Inhibitor	CLINICAL AND APPLIED THROMBOSIS-HEMOSTASIS	2009	10.1177/1076029609343004	256	17,07
46	Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study	BMJ-BRITISH MEDICAL JOURNAL	2015	10.1136/bmj.h1857	254	28,22
47	Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation	CIRCULATION	2011	10.1161/CIRCULATIONAHA.110.985655	253	19,46
48	Dabigatran Etexilate A New Oral Thrombin Inhibitor	CIRCULATION	2011	10.1161/CIRCULATIONAHA.110.004424	252	19,38
49	Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial	LANCET	2015	10.1016/S0140-6736(15)60732-2	251	27,89
50	Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial	JOURNAL OF THROMBOSIS AND HAEMOSTASIS	2011	10.1111/j.1538-7836.2011.04498.x	251	19,31

Table 2. List of top 5 countries by publication frequency in T50

	Country	Frequency
1	USA	36
2	GERMANY	32
3	CANADA	23
4	SWEDEN	23
5	NETHERLANDS	16

Data for the five most influential institutions are shown in Table 3. In T50, Boehringer Ingelheim was the most influential institution, with 37 articles, 761 citations per article, 28,157 citations, and an annual citation average of 1,482. The network map showing the interaction between these organizations is shown in Figure 3.

Table 3. List of top 5 institutions by publication frequency in T50

	Institution	Country	Frequency
1	BOEHRINGER INGELHEIM	GERMANY	37
2	MCMASTER UNIVERSITY	CANADA	19
3	UPPSALA UNIVERSITY	SWEEDEN	16
4	POPULATION HEALTH RESEARCH INSTITUTE	CANADA	13
5	LANKENAU MEDICAL CENTER	USA	11

The data of the five most influential authors are shown in Table 4. Wallentin Lars from Uppsala University was the most influential author in T50, with 14 articles, 967 citations per article, 13,532 citations, and an average of 846 citations per year. The visualized density map of the authors is shown in Figure 4.

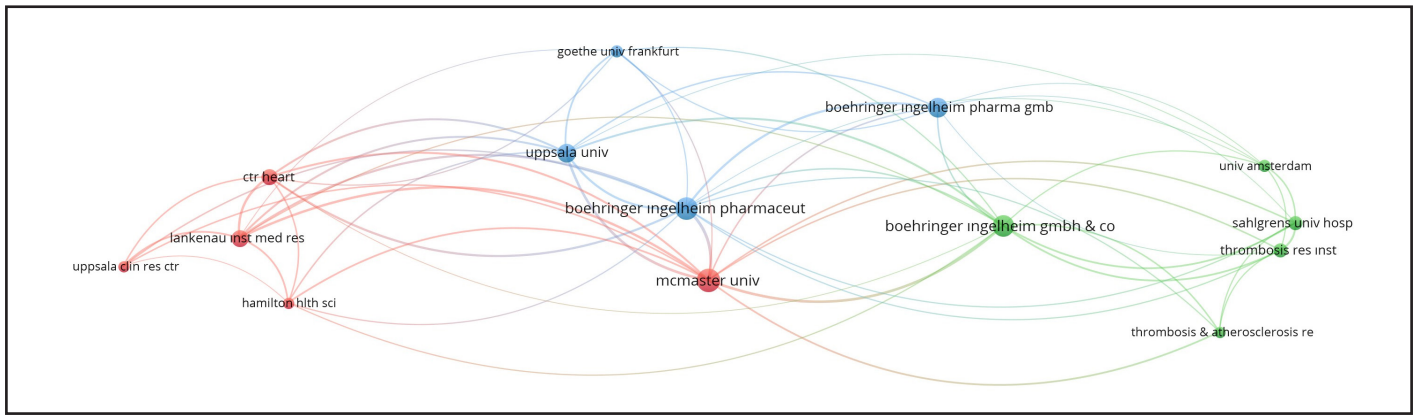

Figure 3. Network visualization map of institution co-authorship

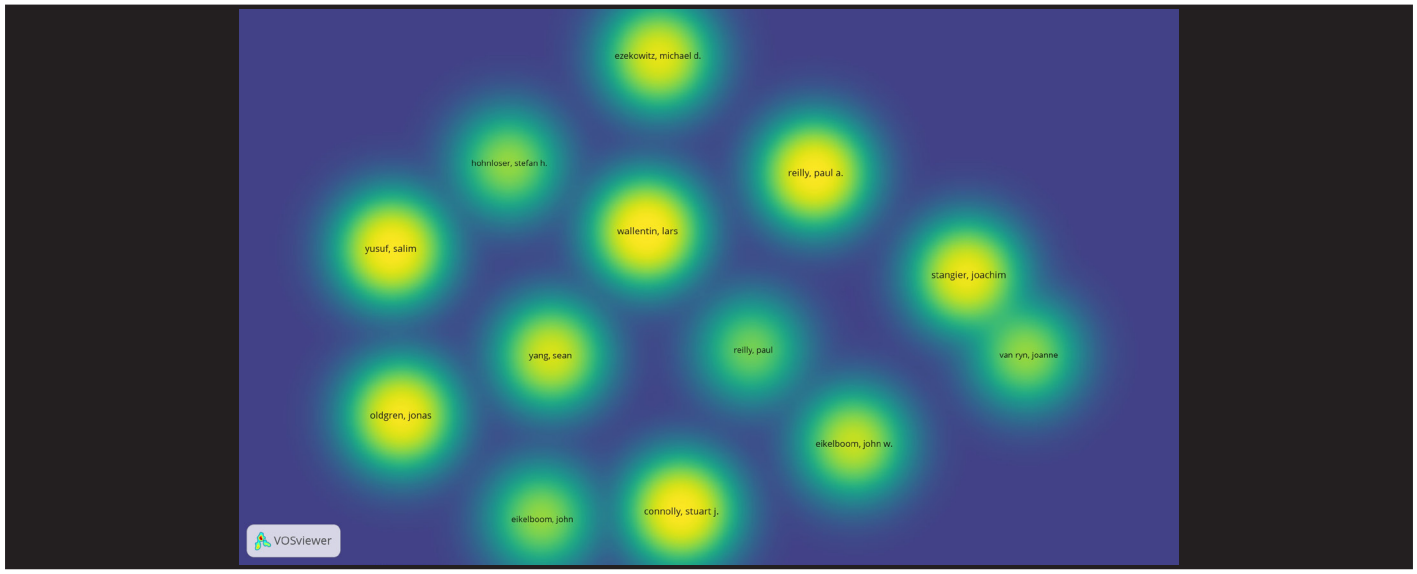

Figure 4. Density visualization map of bibliographic coupling of the authors

Table 4. Data on the top 5 authors with the most publications in T50

Author	Institution	Country	Publications (n)
Wallentin Lars	Uppsala University	SWEDEN	14
Connolly Stuart	McMaster University	CANADA	13
Reilly Paul	Boehringer Ingelheim	USA	13
Salim Yusuf	McMaster University	CANADA	13
Oldgren Jonas	Uppsala University	SWEDEN	11

Table 5. List of top 5 journals by publication frequency in T50

	Journal Name	Frequency
1	CIRCULATION	11
2	NEW ENGLAND JOURNAL OF MEDICINE	9
3	THROMBOSIS AND HAEMOSTASIS	5
4	JOURNAL OF THROMBOSIS AND HAEMOSTASIS	3
5	LANCET	3

Data for the five most productive journals are shown in Table 5. T50 was published in a total of 20 journals. The *Circulation* journal was the most prolific, with a total of 11 articles. It was followed by the *New England Journal of Medicine* (9 articles) and *Thrombosis and Haemostasis* (5 articles). The visualized density map of the journals is shown in Figure 5.

When articles were classified according to T50 WoS categories, the "Peripheral Vascular Disease" category ranked first with 22 articles. This category was followed by "Cardiac Cardiovascular Systems" with 17 articles and "Medicine General Internal" with 15 articles. There were only three articles in the "Clinical Neurology" category.

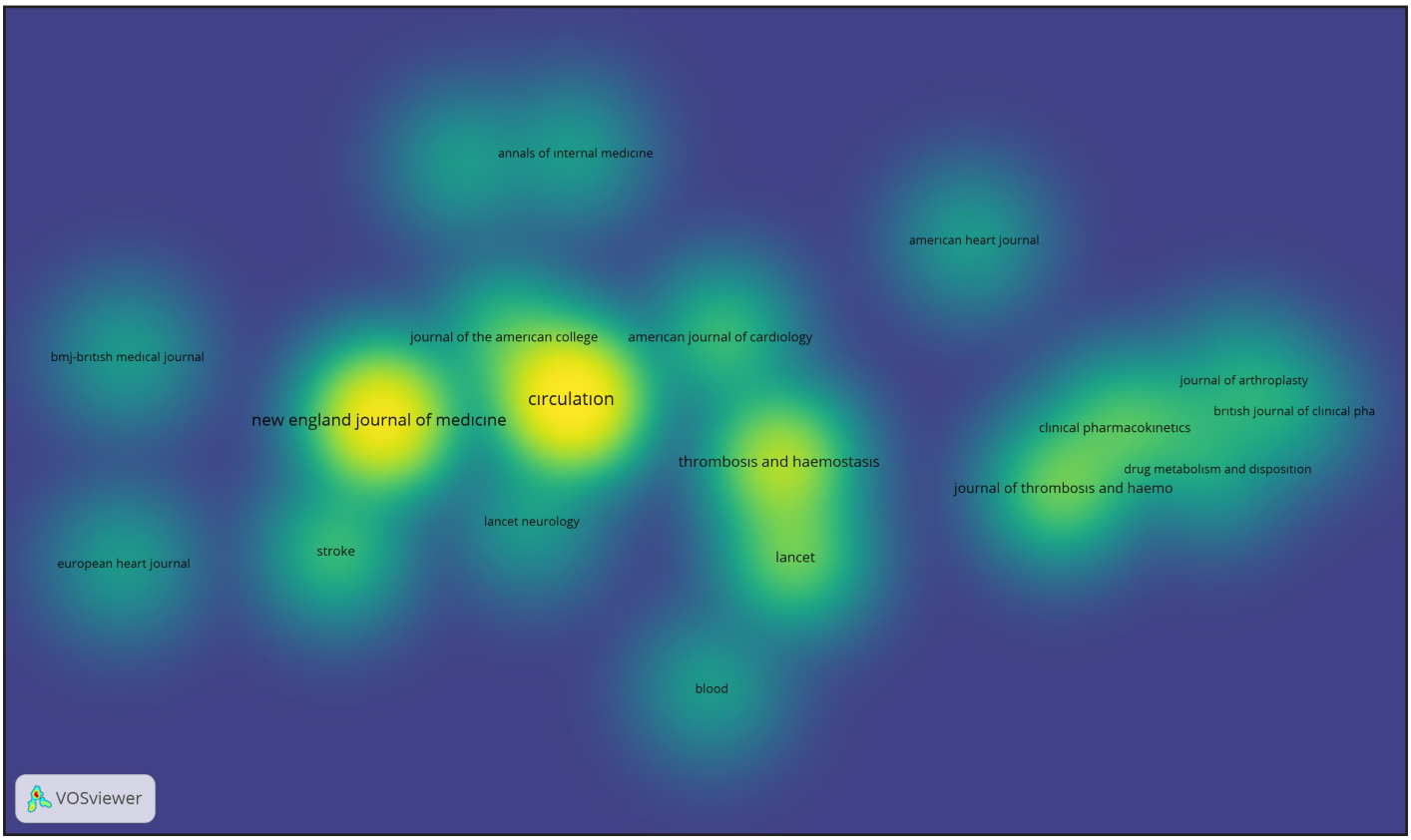

Figure 5. Density visualization map of bibliographic coupling of the journals

DISCUSSION

Science, which has developed with the contribution of countless scientists from ancient times to the present day, has reached a wide audience with the contribution of scientific publications in recent centuries. Bibliometric analysis is one of the quantitative methods that can be used to assess the number and quality of publications in a given scientific field through mathematical and statistical methods [15,16]. Although bibliometric studies are

often criticized for their limited analysis and methodology, they are valuable in reflecting developments and trends in a particular field. In particular, bibliometric analysis of the most cited articles can provide researchers and clinicians with important information about landmark articles [17]. In this way, we think that we will contribute to the literature by analyzing the most cited articles about dabigatran. There is no bibliometric study on dabigatran in the literature.

The number of citations of a study is a relatively reasonable indicator of its quality. The number of citations may vary according to year of publication, frequency of publication of the journal, and the IF of the journal in which the study was published. When a published article is cited 100 times or more, it is considered "classic" in the field of research in which it appears [18]. The number of citations for the top 50 studies ranged from 251 to 7907. Therefore, all of them could be considered "classics" in the field.

As in many previous bibliometric studies, Among T50 articles, the USA ranked first in terms of effectiveness. The USA is the most productive country in bibliometric analyses, from multiple sclerosis and stroke to neurocritical intensive care [11]. The huge financial opportunity of the American scientific community is a major contributor to this. In addition, US authors who have established themselves in the wider scientific community prefer journals in their own country when publishing and citing an article. Besides, the fact that the density of academic institutions and population in the USA is higher than in other countries can be considered as a factor here. After the USA, European countries such as Germany, Sweden, and the Netherlands followed. Participation in the T50 from Asia and Australia was rare. There were no papers from Africa in the T50. There are geographical disparities in scientific production on the subject. There is a need to allocate a global budget for health service financing in countries with socioeconomic inadequacies and to develop scientific cooperation with institutions, journals, and authors in these regions.

The article "Dabigatran versus Warfarin in Patients with Atrial Fibrillation" topped the citation list with 7,909 citations. The study was published in the *New England Journal of Medicine* and paved the way for dabigatran to be approved for clinical use [8]. Therefore, it was not surprising that the explosion of citations for dabigatran came from this study. Following this pilot study, 2011 was the year with the highest number of annual dabigatran publications, while 2013 was the year with the highest number of annual citations.

When T50 articles were classified according to WoS categories, the ''Peripheral Vascular Disease,'' ''Cardiac Cardiovascular Systems,'' and ''Medicine General Internal'' categories were in the top three. Only three articles were in the "Clinical Neurology" category. Although AF is a clinical entity that primarily concerns cardiology, it is a rhythm disorder that every neurologist should recognize. Ischemic stroke prophylaxis in patients with AF is as much a neurologist's concern as a cardiologist's. Thus, it is surprising that there are so few publications in the neurological sciences category among the T50 articles. This may be due to the social security options neurologists face in prescribing and reporting dabigatran, as in Turkey. Solving this problem may increase the number of publications in the neurological sciences category.

Limitation

This study has some limitations. First, the inclusion of only English language original research and reviews from a single database and indexing category may have excluded some publications. Second, the WoS database is constantly updated with new publications. A study conducted at a different time may have different results. Third, the idea that the number of citations a publication receives indicates its quality is controversial. Finally, the citation analysis can bring some biases to mind. Factors such as the language of an article, the year of publication, the IF of the journal, and whether it is open access or not can directly affect the number of citations.

CONCLUSION

This study analyzed the 50 most-cited articles on dabigatran. It highlighted the current status of dabigatran in the literature with information on the most cited publications, the countries involved, and the researchers and institutions involved. The most prolific country was the USA, author was Wallentin, and journal was *Circulation*. This data may help researchers and clinicians access classical publications efficiently and easily.

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Original Research

Breast Stereotactic Excision Results

Zehra Unal Ozdemir[1], Mehmet Onur Gul[2]

[1] Department of General Surgery, Haydarpaşa Numune Training and Research Hospital, University of Health Sciences, Istanbul, Turkey
[2] Department of Surgical Oncology, Malatya Training and Research Hospital, Malatya, Turkey

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Correspondence
Zehra Unal Ozdemir, MD
Address: Department of General Surgery Faculty of Medicine, University of Health Sciences, Istanbul, Turkey
E-mail: drzehraunal@gmail.com

ABSTRACT

Objective: Suspicious microcalcifications detected in mammographic examinations may appear as early signs of breast malignancies. Microcalcifications that appear only on mammography and are not accompanied by any ultrasonographic mass should be excised after marking with a stereotactic wire, and pathological examination should be performed. In this study, we aimed to analyze the stereotactic biopsy results and share their findings.

Methods: Lesions with suspicious microcalcifications on mammography (Figure 1) and in which no mass image was detected in the ultrasonographic response were evaluated retrospectively between January 2016 and December 2022. Excision was applied to the patients after marking with mammography and stereotactic wire. Removal of the suspicious microcalcification area was confirmed by radiography of the specimen in all patients. Pathological examination results of the patients, whether re-excision was made, tumor diameter in cases with malignancy, and follow-up periods of the patients were evaluated.

Results: A total of 54 patients who underwent excision due to microcalcification were evaluated in the study. Malignancy was detected in 15 (27.7%) patients. The most common ductal carcinoma in situ (DCIS) was detected. Re-excision was performed in 4 (26.6%) patients, and mastectomy was performed in 2 (13.3%) patients with malignancy. The median tumor diameter of malignant lesions was 9 mm. The mean follow-up period of the patients was found to be 42.46+16.44 months.

Conclusion: Suspicious microcalcification areas detected in mammographic examinations, lack of ultrasonographic visibility, and biopsy with another minimally invasive method should be excised after marking with a stereotactic wire. This procedure is an effective method that allows early diagnosis of malignancies.

Keywords: Malignancy, mammography, microcalcification, stereotactic excision

INTRODUCTION

The widespread use of mammography scans facilitates the detection of nonpalpable breast lesions and early diagnosis by biopsy. Microcalcifications are frequently seen among mammography findings, and they can be detected in benign as well as malignant cases [1,2]. Excisions performed with wire localization in suspicious breast pathologies accompanied by microcalcifications, which cannot be detected ultrasonographically, contribute to diagnosing malignant cases at an early stage. The 5-year survival of these cases, which are diagnosed at an early stage, can reach 100% [3]. Ductal carcinoma in situ (DCIS) is usually diagnosed by mammography, and it can create an appearance characterized by structural distortion and asymmetrical appearance in the breast, especially

microcalcifications [2,4,5]. There has been reported a 25-30% decrease in breast cancer mortality in women aged 50 to 74 years in Europe with mammography screening programs [6].

In this study, the results of excisional biopsy performed with stereotactic wire localization in breast pathologies with suspicious microcalcifications on mammography but in which no mass image was detected in the ultrasonographic response were analyzed retrospectively.

MATERIALS AND METHODS

This study was designed retrospectively, and ethical approval was obtained (2023-222194649). Female patients who underwent mammography-guided stereotactic marking and excisional biopsy on the same day between January 2016 and December 2022 were included in the study. None of these patients had been previously treated for diagnostic purposes. There is no ultrasonographic equivalent of these lesions. Removal of the microcalcification area was confirmed by radiography of the specimen in all patients (Figure 2). The excision area was marked with clips due to the possibility of radiotherapy necessity. After excision, an x-ray examination of the specimen should be done, and then the specimen should be sent for pathological examination. The removed nonpalpable microcalcification areas were checked with X-ray after the surgical procedure.

In all of these patients, it was determined that the lesions were Breast Imaging Reporting and Data System (BI-RADS) 4 and above and had no ultrasonographic counterparts. The age of the patients, which breast the lesion was in, whether the lesion was benign or malignant as a result of histopathological examination, the diameter of the tumor in cases with malignancy, the follow-up times, and whether re-excision was performed were recorded.

In the preoperative period, 1 gram of cefazolin was administered intravascularly to all patients just before the operation. No patient developed postoperative wound infection, pulmonary complications, or seroma. DCIS patients diagnosed with ultrasonographic trucut biopsy but not palpable on examination and excised by stereotactic biopsy were not included in the study.

Main Points;

- Excision and histopathological examination of suspicious microcalcification areas detected on mammography but not corresponding with ultrasonography are recommended due to their malignant potential.

Statistical Analysis

For statistical analysis, SPSS for Windows version 22.0 package software was used. Descriptive statistics include mean and standard deviation for numerical variables and number and percentage values for categorical variables. The Pearson correlation coefficient was used to test relations between numeric variables.

RESULTS

A total of 54 patients were included in this study. The mean age of the patients was 51.77+7.96 years. It was determined that 25 (46.2%) of the lesions were in the right breast, and 29 (53.7%) were in the left breast. It was determined that specimen radiographs confirmed microcalcification areas in all patients. While benign lesions were detected in 39 (72.2%) patients, malignancy was detected in 15 (27.7%) patients. Only DCIS was detected in 11 (73.3%) malignant cases, invasive breast carcinoma, and DCIS coexistence in 2 (13.3%), and only invasive breast cancer was detected in 2 of them. It was determined that re-excision was performed in 4 (26.6%) of the patients with malignancy due to the proximity of the surgical margin or the continuation of the malignant lesion at the surgical margin. It was determined that all patients who underwent this re-excision were only cases with DCIS. It was determined that 2 of these four patients underwent re-excision because of the presence of DCIS at the surgical margin, and 2 of them due to the presence of DCIS close to the surgical margin.

In 2 of the patients who underwent re-excision, reconstruction was performed with an intraglandular flap. No deformity developed in these patients after radiotherapy (Figure 3).

Subcutaneous mastectomy was performed, and a prosthesis was placed in 2 patients (13.3%) due to extensive DCIS. DCIS could not be detected in the resection specimens of 4 patients who underwent re-excision. In 2 patients who underwent a mastectomy, residual DCIS was seen in several foci around the pouch. The median of malignant lesions was 9 mm (5-45 mm). The mean follow-up period of the patients was 42.46+16.44 months (Table 1).

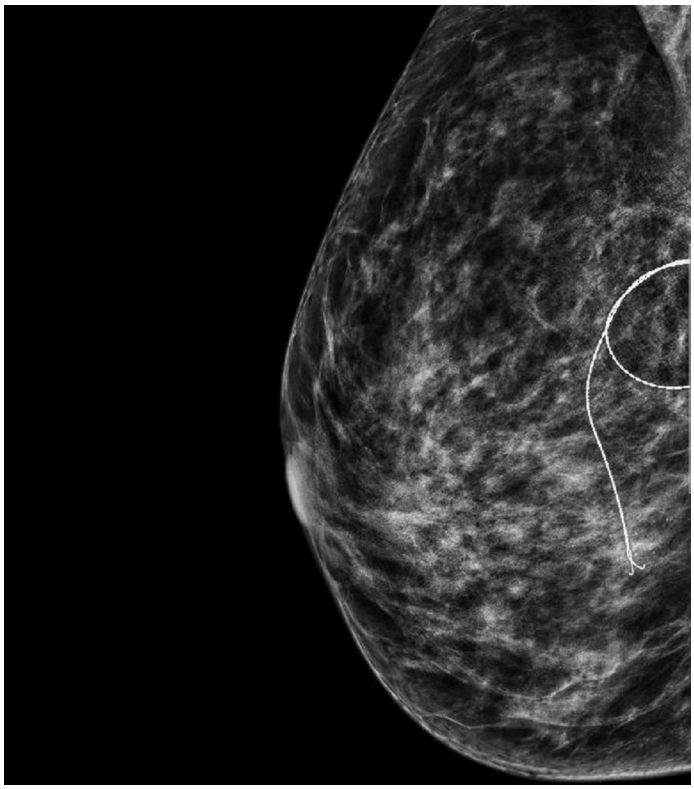

Figure 1. Wire-marked view of the microcalcification area.

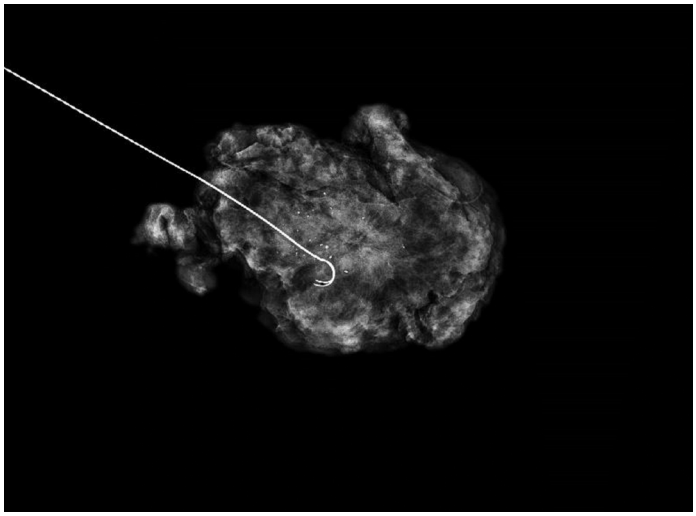

Figure 2. Graph of the specimen. Removed area of microcalcification.

Table 1. Malignant lesion distribution

Histopathology	n	%	Re-excision(n)	Mastectomy(n)
DCIS	11	73.3	4	2
DCIS+Invasive tumor	2	13.3	0	0
Invasive tumor	2	13.3	0	0

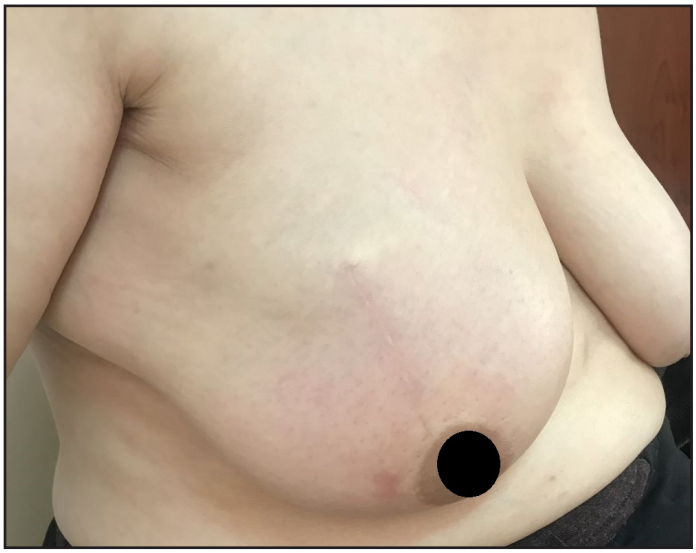

Figure 3. Post-RT image of a patient with a diagnosis of pure dcis who underwent reexcision + intraglandular flap due to proximity to the surgical margin.

Patients with invasive carcinoma were reoperated, and sentinel lymph node biopsy was performed. In one of these patients, axillary dissection was performed after the sentinel lymph node biopsy was positive. Of 54 patients, 25 were defined as BIRADS 4A, 8 as BIRADS 4B, 7 as BIRADS 4C, one as BIRADS 5, and 13 as BIRADS 4, and its subgroups were not specified. DCIS was detected in 3 (12%) of 25 patients with BIRADS 4A. Among eight patients with BIRADS 4B, DCIS was seen in 3 patients, invasive ductal carcinoma in one patient, tubular carcinoma+DCIS in one patient, and the malignancy rate was 62.5% in the BIRADS 4B category. DCIS was detected in 5 (71.4%) 7 patients with BIRADS 4C. Invasive ductal carcinoma was seen in a patient with BIRADS 5. Invasive ductal carcinoma+DCIS was detected in one (7.6%) of 13 patients specified only as BIRADS 4 without identifying the subgroup. Malignancy was detected in 15 (27.7%) of these 54 patients. Considering the BIRADS categories of these 15 patients, it was seen that 20% of BIRADS 4A, 33.3% of BIRADS 4B, 33.3% of BIRADS 4C, 6.6% of BIRADS 5, and 1 patient (6.6%) were in the BIRADS 4 category without a subgroup.

DISCUSSION

In our study, no recurrence was observed, which is the mean follow-up period of 42.46+16.44 months. While breast pathologies manifest as a palpable mass in patients who do not have routine follow-ups in the late period, they can be detected by radiological examinations in the early stages in patients with periodic follow-ups. With the widespread use of mammographic

tests in women, the advantage of early diagnosis of breast lesions and initiation of treatment in the early period has been achieved. The BIRADS classification defines the level of suspicion of mammographic lesions [7]. The results of the BIRADS classification of lesions affect the clinician's decision about the patient, especially in nonpalpable lesions. In this study, patients who did not undergo any diagnostic intervention before were diagnosed with BIRADS 4 and above nonpalpable lesion in their mammography for the first time and underwent excisional biopsy after stereotactic marking were included in the group.

While calcification is detected in 75% of breast cancers in histopathological examinations, calcification can be seen in 35-40% of them radiologically [8]. Excision of calcifications with radiological suspicion of malignancy is an important treatment modality in the early diagnosis of malignancies. In DCIS cases, which are usually accompanied by pathological microcalcifications, a clean surgical margin, and a good cosmetic result are achieved by excision of microcalcification areas after stereotactic wire marking in the early period [9, 10]. Mortality and morbidity are significantly reduced in these cases removed with a clean surgical margin. Nonpalpable breast lesions can be removed at 90-100% with the excision method after marking with a stereotactic wire [11]. After excision, an x-ray examination of the specimen should be done, and then the specimen should be sent for pathological examination. In this study, the removed nonpalpable microcalcification areas were checked with X-ray after the surgical procedure, and it was confirmed that the microcalcification areas were removed. During the marking process with the stereotactic wire, wire breakage, migration, and infection can be seen. A single prophylactic dose of 1 gram of cefazolin sodium was administered to all patients. No surgical site infection was observed in the patients. These patients did not observe complications such as migration or breakage of the wire inserted with stereotactic marking. The short duration of the surgical procedure after stereotactic marking may also be effective in this.

This study determined that four patients with DCIS underwent re-excision (30.7%), and 2 patients underwent mastectomy (15.3%). It was observed that the rate of re-excision was consistent with the literature, but the rate of mastectomy was lower than the literature [12]. Langhans et al. reported that they found a 3-fold higher re-operation rate in DCIS than in invasive breast cancers [12]. They emphasized that this was because the borders of DCIS were not well defined and could be widespread in the breast. In this study, re-excision was performed in patients with close proximity to the surgical margin and the presence of DCIS at the surgical margin. Still, DCIS could not be detected in the re-excision specimens. In 2 patients who underwent mastectomy for widespread DCIS, DCIS was seen in several foci around the pouch. In surgical margin positivity, mastectomy can be planned by considering the extent of the disease, high grade, and presence of comedo necrosis. In one of the patients who were diagnosed with invasive breast cancer and had sentinel lymph node biopsy, the sentinel lymph node was positive, indicating the importance of studying the sentinel lymph node in invasive breast cancers.

Most DCIS cases are detected due to mammographic examinations, and the standard treatment is surgical procedures [13]. Wapnir et al. reported that local recurrence rates in DCIS cases who underwent breast-conserving surgery were as high as 25%-35% in 13-17 years of follow-up, and half of these recurrences were seen as invasive cancer and expressed by. The same study demonstrates the importance of long-term follow-up of DCIS cases in terms of local recurrence after surgery [14]. In our study, no recurrence was observed, which is the mean follow-up period of 42.46+16.44 months. The mean follow-up period in malignant patients was found to be 42.73+17.58 months. DCIS, which is seen in approximately one in 33 women throughout life, peaks around the age of 50, and its incidence decreases rapidly after the 7th decade [15].

Microcalcifications are generally one of the earliest signs of breast cancer that mammography can detect. Malignant microcalcifications have a clustered pleomorphic appearance and vary in size and density. They can be segmental, linear, and branched structures and show interval changes [1]. Accurate interpretation of microcalcifications observed in mammography is critical. In this way, appropriate action plans such as advanced diagnostic tests and biopsies will be determined. By detecting microcalcifications at an early stage, the chance of early diagnosis of breast cancer will be achieved. Stereotactic excision is a surgical procedure that enables the effective removal of breast microcalcifications. Extensive resection to obtain a clean surgical margin may result in the loss of intact breast tissue and adverse cosmetic results.

CONCLUSIONS

In suspicious microcalcifications that only show mammographic findings, a biopsy can be performed by excision method after

marking with stereotactic wire. Excision of the pathological microcalcification area should be confirmed by x-ray after the surgical procedure. It should be remembered that re-excision may be required due to histopathological examination, especially in DCIS cases. Microcalcifications observed on mammography should be carefully examined because of their importance in early breast cancer diagnosis.

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Review

Rehabilitation in Spinal Muscular Atrophy: A Narrative Review

Seth Kwame Agyenkwa[1], Pınar Cibooğlu[1], Nour Jhar[1], Ahmet Abo Orabi[1], Rustem Mustafaoglu[2]

[1] Department of Physiotherapy and Rehabilitation, Institute of Graduate Studies, Istanbul University-Cerrahpasa, Istanbul, Turkey
[2] Department of Physiotherapy and Rehabilitation, Division of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Istanbul University-Cerrahpasa, Istanbul, Turkey

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Correspondence
Agyenkwa, Seth Kwame
Address: Üniversite Mahallesi Bağlariçi Caddesi No:7, 34320 Avcılar/İstanbul.
E-mail:
sethkwameagyenkwa@ogr.iuc.edu.tr

ABSTRACT

Spinal muscular atrophy (SMA) is a group of genetic diseases that cause muscle weakness and mobility problems. There are no clear clinical guidelines for assessing and rehabilitating individuals with SMA, despite its increasing prevalence. This study aimed to provide a comprehensive review of physical therapy's effectiveness in improving treatment outcomes for SMA by analyzing existing literature. A search was conducted in Pubmed, PEDro and Google scholar using relevant keywords. Studies on assessment, treatment, and rehabilitation for SMA were included in the review. The review found that assessment must be comprehensive, and rehabilitation approaches include exercise training, positioning, orthotics, and mobility aids, chest physiotherapy, contracture and scoliosis management, and aquatic exercises. Physical therapy improves the quality of life for children with SMA at every stage of the disease. However, there is still insufficient evidence on the effectiveness of physical therapy in managing people with SMA, and more high-quality studies are needed.

Keywords: Spinal muscular atrophy, exercise, rehabilitation, review

INTRODUCTION

Spinal muscular atrophy (SMA) is a hereditary disease that damages motor neurons in the spinal cord and brain stem, leading to muscle weakness and atrophy. This results in difficulty with essential skeletal muscle activities such as speaking, walking, breathing, and swallowing [1]. The condition, which was first described by Guido Werdnig and Johann Hoffsman in the 18th century is characterized by the degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis [2]. SMA is an autosomal recessive disorder that results from a homozygous deletion or mutation in the gene 5q13 survival motor neuron (SMN1) gene [3]. There are four known types of SMA, with decreasing severity from Type I, also known as the Werdnig-Hoffman disease to Type IV according to the age of onset, highest level of motor function and prognosis [4].

Literature on SMA's prevalence and incidence is rare. The National Organization of Rare Diseases reports that SMA has an overall incidence of approximately 1 in 10,000 live births, which means 10 in 100,000 live births. Despite the generally low prevalence of SMA, relatively high prevalence was observed in studies from Italy and Scandinavia with a prevalence of 6.56 per 100.000 persons under 20 years and 4.18 per 100.000 persons under 18 years respectively [5]. In Canada, no exact prevalent study has been reported, but it is estimated that 37.2 new cases of all SMA subtypes are reported annually [4]. There are higher estimates of the incidence of SMA among countries where consanguineous marriages are common [6, 7]. About 69% of people affected by SMA in Turkey had a history of consanguineous marriages [7]. Also in Saudi Arabia, a prevalence of 13.26 per 100.000 live births were reported [5].

SMA is second to cystic fibrosis on the list of common fatal autosome recessive disorder, and among children regarded as the most common genetic cause of death [5].

The complex nature of the clinical manifestation and associated difficulties in the diagnosis of SMA necessitates a multidisciplinary intervention that comprises of experts with the competencies in managing the pulmonary, gastroenterology or nutrition and orthopedic complications of the condition. SMA depending on the type and severity may be marked with severe hypotonia, symmetrical flaccid paralysis, respiratory insufficiencies, joint contractures, kyphoscoliosis, weakness in masticatory muscles which results in difficulties in chewing and swallowing[2]. Pharmacologically, disease-modifying drugs such as Nusinersen (Spinraza) which was the first to be approved in the United States by the FDA in 2016, Zolgensma in 2019 and Risdiplam (Evrisdy) in 2020 are used in the treatment of this incurable condition[8, 9]. Studies have showed the effectiveness of the Nusinersen through augmentation in the production of functional SMN protein [8, 10]. Physical therapy using exercise, electrotherapy, aqua-therapy, and other modalities may enhance outcomes such as quality of life, social integration, and independence of persons with SMA. The evidence regarding physical exercises for SMA type III is unclear, with only few studies [11].

The literature on assessment and treatment of SMA with physical therapy is insufficient. Therefore, there is a lack of clinical practice guidelines that guide physical therapists on the assessment or treatment of children and adolescents who survive SMA. The review aims to provide a comprehensive understanding of physical therapy in improving the treatment outcomes of children with SMA through assessment, best treatment, and evaluation by exploring the existing literature.

Pathophysiology

The precise function of the SMN protein in neuronal function and development is unknown, and its absence causes such severe impairments that detailed pathophysiological explanations have evaded us thus far. In youngsters, the severity of SMA varies. Only a tiny portion of the SMN messenger RNA (mRNA) transcript produced by the SMN1 gene is composed of the SMN2 gene. The severity of the condition is inversely related to the number of copies of the SMN2 gene [12]. Individuals with severe SMA type I who had sural nerve biopsy had significant sensory nerve pathology, but patients with milder SMA types II or III had no sensory nerve abnormalities clinically or morphologically [13]. The SMN protein is found in all eukaryotic cells and has proven to serve a critical function in homeostatic cellular pathways in all cells. SMA is divided into four phenotypes based on the age of onset and the level of the motor function obtained [3] (Table 1).

Table 1. The SMA phenotypes

Type	Definition
SMA type 0	This is a rare type. Early respiratory failure, significant weakness, and often decreased fetal movements accompanying arthrogryposis can be seen in the neonatal period. Death occurs most frequently during birth or within the first month of life.
SMA type I	Is the most prevalent, and children may never be able to sit independently. Hypotonia and areflexia are present in the first six months of infancy, and their cognitive development is normal, and their expressive gaze contrasts with their paralytic attitude. Intercostal muscle involvement predominates, and brainstem involvement can also occur, which are significant characteristics of the condition.
SMA type II	Symptoms emerge between the ages of 6 and 18 months; children may sit, and some can even stand, but they will not be able to walk independently and suffer from a gradual proximal weakness that disproportionately affects the legs rather than the arms. Restrictive lung disease may be caused by progressive scoliosis and the weakening of the intercostal muscles. Patients may live to 25 years, a few live till their third decade; respiratory failure is the leading cause of death.
SMA type III	Usually achieve all the major motor milestones, including independent walking. **Patients will have muscle exhaustion, progressive weakening, and atrophy of the lower limbs.** Visceral involvement is more common in this type. Hypotonia, hyperlaxity, and the lack of osteo-tendinous reflexes are all common symptoms. Patients rarely develop restrictive lung disease, and their life expectancy is unaffected
SMA type IV	Patients who can walk in adulthood and have no respiratory or dietary issues fall into this category. The last category includes SMA type IV, which represents a mild course, and adult-onset (> 18 years) patients. This category includes patients who can walk in adulthood and have no respiratory or nutritional problems. This phenotype of SMA affects adults (over 21 years of age) and is the mildest of the SMA phenotypes. The patients are ambulatory and have mild leg weakness that progresses to proximal weakness. In most cases, life expectancy is unchanged.

Diagnosis

Clinically, patients with SMA have significant hypotonia and proximal weakness. The weakness is usually symmetrical and affect the legs more than the arms. There is also weakness in the bulbar, intercostal, and fascial muscles. Weakness of the intercostal muscles results in the typical bell-shaped chest and paradoxical breathing pattern. In addition, these patients have absent or decreased tendon reflexes [14]. The standard tool for diagnosing SMA is molecular genetic testing. Molecular testing is highly efficient and SMA is observed frequently in hypotonic or "floppy" infants [15]. Creatine Kinase (CK) and electromyography (EMG) are used in the diagnosis of SMA. For a patient suspected of having SMA, the initial diagnostic test to look out for is the homozygous deletion of the SMN1 gene. There is a characteristic homozygous absence of exons 7 and 8 of the SMN1 gene, or in some instances, only exon 7 in majority of patients with SMA [16].

The results of electro-diagnostic studies display diverse characteristics of motor neuron or axon loss, which are in accordance with the impairment of motor neuron function. EMG is typically unnecessary for children with type I and II SMA; however, it can be useful for chronic forms in which the phenotype may not be as noticeable. While CK serum levels are generally normal or only slightly elevated in SMA, there have been a few cases where levels were significantly elevated (up to 10 times). As a result, a normal CK level does not necessarily rule out a diagnosis of SMA [17].

Complications

The focus of treating and managing SMA is to prevent or treat complications caused by weakness while also maintaining the individual's quality of life. Weakness can affect various body systems, including the respiratory system, leading to breathing problems, the gastrointestinal system, causing difficulty swallowing and constipation, and the musculoskeletal system, resulting in mobility issues [18]. Respiratory insufficiency is the primary cause of morbidity and mortality in patients with SMA type II. Primary complications include ineffective coughing causing reduced airway clearance, impaired lung and chest wall development, and an increased risk of pulmonary infections. Nocturnal hypoventilation is also a common problem [19]. In the absence of ventilation assistance, children with SMA type I typically do not survive beyond the first two years of life. However, for type IIa and IIb, the estimated survival rates are 81% and 67.7%, respectively, without the need for ventilation assistance [20]. Patients also experience a diminished health-related quality of life that is lower when compared to the general healthy population [21, 22]. Caregivers also report the need for respite care, physiotherapy from injuries, sleep disturbances and work adjustments [22].

Functional Assessment

To assess patients with SMA, a comprehensive physical examination is recommended to evaluate structural and physical impairments or disabilities, social participation, and environmental integration, as well as participation in basic functional and instrumental activities of daily living. This assessment should follow the International Classification for Functioning Disability and Health (ICF) guidelines to cover all relevant aspects based on the patient's age and level of severity. Clinical evaluation in SMA patients should include the musculoskeletal, neuromuscular, and pulmonary systems. This may include assessments for strength and range of joint motion, as well as the use of relevant motor functional scales and timed tests to monitor the aspects of function that reflect the patient's ability to carry out daily activities [23]. To assess hypoventilation in patients with SMA, a range of techniques can be used, including spirometry, forced oscillation technique (FOT), lung clearance index (LCI), evaluation of signs of nocturnal hypoventilation and respiratory muscle strength, swallow function assessment, chest x-ray, and sleep study. Volitional or non-volitional spirometry tests are commonly used in clinical practice to assess respiratory muscles. These tests include vital capacity (VC), maximal static pressures, sniff nasal inspiratory pressure (SNIP), peak expiratory flow (PEF), and peak cough flow (PCF) [24]. Spirometry and FOT testing are applicable in children with SMA as young as three years old. Vital capacity (VC) is the primary test used to assess respiratory function in children with SMA. Peak cough flow (PCF) and maximal static inspiratory and expiratory pressures are used to monitor cough efficiency and respiratory strength. Polysomnography (PSG) is used to evaluate sleep patterns, breathing, and the use of non-invasive ventilation (NIV) in pediatric SMA patients [25]. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Functional Motor Scale (HFMSE), Revised Upper Limb Module (RULM), and Hammersmith Infant Neurological Examination (HINE) are commonly used scales for assessing the functional status of children with SMA. These scales are used based on the patient's level of function, which can be classified as non-sitters, sitters, and ambulant [26].

Rehabilitative Approaches to Managing SMA

Exercise Training

Exercise training is important in managing SMA to protect muscles from wasting, improve cardiorespiratory function and physical fitness, and prevent contractures. A study demonstrated that progressive resistance training exercise is safe and well tolerated in children with SMA. The study involved nine children with SMA who completed 12 weeks of home-based progressive resistance training with supervision. Significant improvements were observed in the total composite score of manual muscle testing (MMT), but no significant changes were reported in quantitative muscle analysis and hand-held dynamometry (HHD) measures [27]. A study involving 14 patients with SMA found that a home-based cycling and strength training program could be tolerated and performed safely by children with SMA and had the potential to increase their maximum aerobic capacity (VO2 max) within six months. However, no significant changes were observed in measures such as fatigue, quality of life, strength or motor function, or distance walked on the six-minute-walk-test (6MWT) after the six-month period [28]. A study involving six SMA III patients who underwent 12 weeks of cycle ergometer training reported an improvement in VO2 max, but there were no significant changes in muscle strength or increased activities of daily living [29]. All these studies involved relatively fewer numbers of patients with SMA.

A recent Cochrane review found no significant difference in improvement of walking distance or quality of life between an exercise group and a usual care group. Additionally, there was no significant difference in VO2 max between the two groups [30]. A study showed that 92.4% of the respondents recommended stretching interventions. Among the modalities to encourage stretching, standers or standing frames, passive stretching, daytime splinting/bracing, nighttime splinting/bracing, active-assisted stretching, positioning in prone/on a wedge and active stretching were the most prevalent [31]. The recommended duration of stretching to improve length is up to 60 minutes and should be held at an end range greater than 60 degrees. The recommended frequency of stretching varies based on the functional status of the patient, with a minimum of three to five times per week for non-sitters, five to seven times per week for sitters, two to three times per week for ambulators, and three to five times per week for optimal ambulators [23]. Furthermore, the combination of pharmacotherapy Nusinersen, with exercise training in patients with SMA is more effective in improving motor skills than using only pharmacological treatments [32].

Positioning and Orthotics

Muscle strength and mobility are common difficulties in children with SMA. Pediatric orthotics can assist these children in moving around and performing other duties. Orthotic treatment is crucial in dealing with muscle weakness. Ankle foot orthoses (AFOs), knee-ankle-foot orthoses (KAFOs) and hip-ankle-knee-foot orthoses (HKAFOs) enable children to maintain proper joint alignment during walking or standing. Corset braces, thoracolumbarsacral orthosis (TLSO), and cervical-thoracolumbarsacral orthosis (CTLSO) provide postural support to reduce undesired movements and deformities. Neck immobilization is important for transportation safety. Orthotics should be worn at least five times a week and removed 60 minutes before bedtime. The patient's vertical position should be maintained for no more than 60 minutes, with a minimum of 3–5 times per week and a maximum of 5–7 times per week [33, 34]. Different methods, such as orthoses, splints, active or passive positioning, and phased gypsum casting procedures, can be used to retract the muscles of the axial skeleton and limbs. Verticalization can be achieved with the use of TLSO corsets, KAFO splints, or individual HKAFO devices. A Shant's collar is often used to fix the neck in an upright position to reduce the risk of suffocation and regulate the head [28]. Seating and orthostatic support systems should include components for maintaining a proper sitting position such as molded cushions and supports. Individualized wheelchairs and sleeping arrangements are advised. Wheelchairs with a falling/tilting back, customized seats, and neck braces may be used for daily movement and transit. TLSO corsets with an abdominal window are recommended for respiratory support [33].

Use of Mobility Aids

For patients with limited stamina, lightweight manual wheelchairs or motorized wheelchairs can be used to facilitate mobility. Power wheelchairs or motorized scooters may be used for long distances. Patients who can only be verticalized in a sitting position should have motorized wheelchairs or a tailored chair. Motorized wheelchair usage should be evaluated in patients above two years of age [35]. Lightweight manual or power wheelchairs may be recommended for patients with preserved upper limb function and muscular strength. Patients with SMA Type I and Type II may require an adaptable stroller or electric wheelchair, depending on their age. These wheelchairs and strollers can be equipped with critical medical equipment and have customizable controls [23, 36]. To enhance mobility and functional independence in children and adolescents

with SMA, activities such as swimming, hippotherapy, and wheelchair sports should be used in rehabilitation. Aerobics, general exercises, and other activities like walking, cycling, yoga, rowing, and elliptical/cross trainers may also be included under the supervision of a therapist. Horseback riding and wheelchair games can also be used to engage core muscles and promote sitting upright [33].

Chest Physiotherapy

Pulmonary dysfunction and respiratory impairment are the primary cause of mortality in SMA patients, especially in those with types I and II [37]. Patients with type III have a lower incidence of pulmonary failure and better lung function. Regular monitoring of respiratory muscle function is crucial to prevent and treat acute and chronic respiratory failure, as respiratory muscle involvement is a significant factor in children with SMA [38]. Patients with SMA often experience proximal muscular weakness, which may cause a decline in the function of the muscles that control breathing. The progression of scoliosis and chest wall deformity can also lead to a decrease in pulmonary function. However, advancements in spinal/chest wall implant systems, peri-operative critical care management, medical treatments, and physiotherapy/respiratory therapy offer promising outcomes for patients [39].

The main pulmonary approach for patients with neuromuscular disease is mechanical airway-secretion mobilization and clearance, assisted by coughing or mechanical insufflation-insufflation. Airway clearance techniques for congenital muscle disorders involve cough augmentation and mucus mobilization. To protect the airways, techniques such as oral suction and side-lying are indicated [38]. The mechanical in-exsufflator (MI-E) has been found to effectively stimulate normal cough in adults with SMA by providing positive-pressure insufflation with expulsive exsufflation. However, there is insufficient evidence to support its effectiveness in children [40]. Interest is growing in the utility of maximal inspiratory pressure (MIP) as both a therapeutic clinical trial endpoint and an early evaluation tool for assessing respiratory muscle strength in patients with SMA [41]. In non-sitting patients, utilizing a mechanical suction pump and a catheter for oral suctioning is a crucial element of airway clearance [42].

A study involving 34 children (18 SMA and 16 Duchenne Muscular Disease) found that functional vital capacity (FVC) reduction varied across age groups, and scoliosis was present in a significant proportion of patients with both subtypes. Surgery for scoliosis was required for a substantial number of patients. The study also found that FVC was associated with scores on the HFMS and RULM scales, and that noninvasive positive-pressure ventilator support was effective in managing respiratory function in SMA patients undergoing spinal surgery [43]. Continuous Positive Airway Pressure (CPAP) and Bilevel Positive Airway Pressure Support (BIPAP) can be acquired via respiratory aids depending on the severity of the breathing difficulty [44].

Contracture Management

Patients with SMA often experience orthopedic issues like contractures, hip instability, chest deformities, fractures, and scoliosis. Muscle weakness, decreased range of motion, and prolonged static positioning contribute to the development of contractures, which are more common in non-ambulatory individuals with SMA, particularly in the lower extremities [33]. Contractures can result in limited function and pain, significantly affecting daily lives. ROM exercises are crucial in maintaining joint flexibility, reducing the risk of permanent joint shortening and tightening, and ultimately reducing contractures. It is recommended that all SMA patients engage in flexibility and ROM exercises regardless of their level of mobility to improve mobility and reduce pain [45].

Scoliosis Management

More than half of children with SMA develop scoliosis, which is most frequently observed in those who are non-ambulatory or have lost their ability to walk. Approximately 50% of individuals with type III SMA will develop scoliosis, while almost all children with types I and II SMA are affected by scoliosis. Children with SMA frequently develop scoliosis at a young age, often before the age of four [46]. Most children with the disease develop thoracolumbar scoliosis that is C-shaped and progresses at a rate of 5°-15° in Cobb angle [33]. The conservative management of scoliosis in patients with SMA is difficult and the outcomes are typically not satisfactory. Corset therapy is not recommended for ambulatory patients as it can reduce trunk mobility and lead to a potential loss of walking ability. Spinal fusion and bracing are commonly used treatments for scoliosis, but there is no clear consensus on their efficacy [45]. In children with SMA type II, there is a correlation between achieving assisted walking through orthotics and bracing and a decreased risk of developing scoliosis. If scoliosis is left untreated, it can worsen the prognosis for the respiratory system [46].

Aquatherapy

Aquatic therapy or hydrotherapy is recommended as a treatment for SMA patients who can sit or walk, according to the International Standard of Care Committee for SMA [47]. Individuals with SMA type III may partake in aquatic therapy that encompasses exercises aimed at improving their balance, flexibility, strength, posture, and walking. On the other hand, individuals diagnosed with SMA type I may engage in activities that target their respiratory function, such as blowing pingpong balls in the water. Water has unique qualities that enable weight relief and postural support, enhance antigravity movements, and offer children the ability to execute activities that may be beyond their capabilities on land [48]. The importance of aquatherapy in the rehabilitation of children with SMA is provided below (Figure 1).

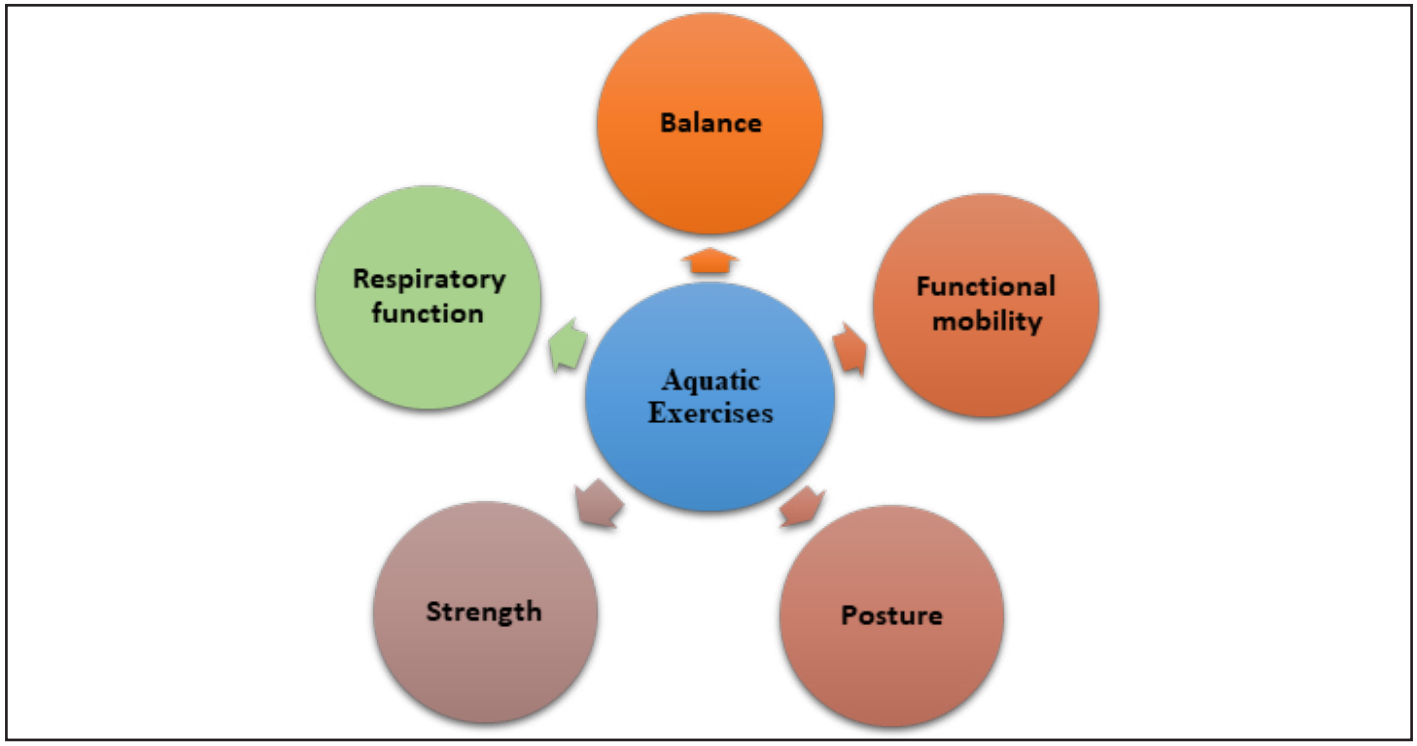

Figure 1. The importance of aquatic therapy for treatment in persons with SMA.

Technology and Ergometric Management

Robot-assisted gait training (RAGT) is a physiotherapy approach that combines robotics and intense repetitive workouts to enhance mobility, but there is insufficient evidence to support its effectiveness in individuals with SMA [49]. The Hybrid Assistive Limb (HAL) is a treatment device that utilizes cybernics to assist walking exercise, and has shown to be more effective than traditional walking approaches in patients with incurable neuromuscular diseases [50]. Cybernics technology integrates the human nervous system and a robot using bioelectric signals. This results in a dynamic state where the wearer and the device are physically and functionally linked, and the device operates based on the wearer's motor intentions and internal ideal movement patterns [51]. The use of Hybrid Assistive Limp (HAL) device, which integrates the human nervous system and a robot through bioelectric signals, resulted in a significant improvement in the distance covered during the two-minute-walk test and cadence total scores during the ten-minute-walk test. The study reported mild adverse effects such as myalgia, back pain, and skin contact issues, which were easily resolved [52].

The Yumen Arm is a new dynamic arm support that can improve the performance of upper extremity tasks in patients with neuromuscular diseases. Studies show that using the Yumen Arm can lead to improvements in active range of motion and functional ability and can make exercise performance less tiring. However, individual subject variability was high, highlighting the importance of tailoring dynamic arm supports to each patient's specific needs [49]. A new approach to evaluate

upper limb function in patients with SMA has been created using the Kinect 3-D sensor. The sensor is portable and cost-effective, and the assessment is designed as a game-like test. The Kinect-based assessment offers a comprehensive and objective movement analysis, while being a low-cost, portable, and child-friendly solution compared to traditional clinical rating scales or marker-based video systems [53].

The Wilmington Robotic Exoskeleton (WREX) is a modular body-powered orthosis that can be easily attached to a wheelchair to enable antigravity, three-dimensional arm movements. Patients who use the WREX and their families reported a substantial improvement in self-feeding. However, the current apparatus does not allow or assist in pronation or supination, which are necessary for the feeding process, and this extra degree of flexibility is being planned for a future version of the WREX [54].

Conclusion and Recommendations

This review provides a comprehensive overview of the management of SMA through physical therapy modalities spanning from conventional physical therapy such as exercise, chest physiotherapy, aqua-therapy and the use of mobility aids, through technological advancements that enhance performance in functional and recreational activities of living. It also provides an update on holistic assessment of deficits and other conditions related to SMA with reference to the ICF system. Physical therapy at every stage of SMA enhances the participation of various life activities, ensures social integration, and thus promote the quality of life of children and adolescents affected by SMA. The evidence supporting the effectives of physical therapy in management of persons with SMA is still inadequate, and therefore we recommend the need for more high quality randomized controlled trials of physical therapy interventions among this population.

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Review

An Introduction to Propensity Score Analysis: Checklist for Clinical Researches

Nazlı Totik Doğan[1], Sevinç Püren Yücel Karakaya[1], Zeliha Nazan Alparslan[1]

[1] Department of Biostatistics, Faculty of Medicine, Çukurova University, Adana, Turkey

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Correspondence
Nazli Totik Dogan
Addresss: Department of Biostatistics, Faculty of Medicine, Çukurova University, Adana, Turkey
E-mail(s): ntotik@cu.edu.tr; nazlitotik.biostat@gmail.com

ABSTRACT

Background: Propensity score analysis is a widely used method to estimate treatment effect in dealing with the selection bias (i.e. lack of randomization) of observational studies. Although, there are relatively many guidelines in the literature for the adoption of this analysis, no checklists exist.

Objective: In this study, we propose a basic guideline for propensity score analysis, a tutorial that may be used to improve the quality of studies which implement this analysis. Additionally, in line with this guideline, we present an easy-to-use checklist which will assist researchers in the analysis process.

Conclusion: In light of the principles in this guideline/checklist, we propose that minor updates be considered for STROBE.

Keywords: Observational study, propensity score, treatment effect, selection bias, STROBE

INTRODUCTION

The most important characteristic of randomized clinical trials (RCTs), which are considered to be the gold standard for assessing the effect of treatments, is randomization [1,2]. On the other hand, RCTs have limitations due to temporal, financial, ethical, logistical or other reasons. To overcome these limitations, applied clinical researchers tend to plan observational studies that provide useful information for addressing health-related questions [3,4,5,6]. In RCTs, since there are randomly allocated similar treatment groups, the effect of treatments is often directly comparable; but, owing to covariate imbalance, such direct comparisons may not be possible in observational studies. Observational studies are frequently vulnerable to selection bias due to the lack of random treatment allocation, and this vulnerability leads to an imprecise estimate of the treatment effect [4,6,7,8]. To control selection bias, the propensity score(PS), described as "the conditional probability of assignment to a particular treatment given a vector of observed covariates" has first been proposed by Rosenbaum and Rubin in 1983 [9].

Over the past decade, PS analysis has gained popularity among clinical researchers. Examples of such studies include evaluating the effect of pancreatoduodenectomy(minimally invasive vs. open) on short-term outcomes among European centers [10]; the effectiveness of a placebo over another placebo in multiple sclerosis[11]; the effect of community pharmacy-based medication on death and readmission after hospital discharge[10,11,12]. Despite its popularity, there is a lack of complete guideline for PS analysis to help applied clinical researchers in the methodology literature [2,13,14]. Thus, in order to contribute to the methodology, we present basic guideline and checklist for the step-by-step implementation of PS analysis.

Stages of PS Analysis

Background

Randomization is not performed in observational studies. Thus, treatment groups generally not being comparable may result in confounding bias. If this happens, an appropriate adjustment should be made for confounding. As the PS summarizes all covariates into a single score, it decreases the potential for overfitting [15].

The PS is theoretically defined as a participant's probability of receiving the treatment conditional on the covariates at baseline. There are many settings in which the treatment may be binary, multinomial, ordinal, or continuous [16]. Let T_i be a binary treatment indicator variable (where T_i equals 1 if the participant is in the treatment group or 0 if the participant is in the control group) and x_i be a vector of observed covariates. Then, for each participant *i*, PS (e_i) is expressed as follows:

$e_i = \Pr(T_i | X_i)$

Strongly ignorable treatment assignment assumption has been proposed by Rosenbaum and Rubin to obtain unbiased treatment effects using PS. This assumption consists of two conditions:

(1) Conditional independence: $Y(1), Y(0) \perp T | X$

(2) Positivity: $0 < P(T=1 \mid X) < 1$

The first condition means that all confounding variables must be known. Lee and Little (2017) state that this condition cannot be tested empirically [13]. Instead, one must be persuaded that all crucial variables are measured in the study design. The second condition means that the individual had a non-null probability to receive treatment [5,6,8,17,18]. PS analyses generally consist of two phases: the design phase (phase I) and the analysis phase (phase II). In the design phase PSs are estimated using the PS model, and in the analysis phase the estimated PSs are used in the treatment effect model to adjust the effect of treatment. The type of the PS model depends on the nature of the treatment, and the treatment effect model on the outcome variable [5]. The stages of these phases are summarized in Table 1.

Table 1. Basic Stages of PS Analysis

Phase I	**Stage 1**	PS Model Building ○ Covariate Selection ○ PS Estimation ○ Checking Overlap ○ First Balance Control
Phase II	**Stage 2**	Application of PS Methods ○ Specifying Treatment Effect ○ PS Methods ○ PS Matching ○ PS Weighting ○ PS Stratification ○ PS Covariate Adjustment ○ Second Balance Control
	Stage 3	Treatment Effect Estimation

PS: Propensity score

Main Points:

- Providing detailed tutorial and design guide for PS analysis
- Contribution to the methodology with easy step-by-step PS analysis implementation
- Allowing to control the quality of PS analysis with the checklist
- Standardizing the reporting of future studies by following the checklist
- Emphasizing consideration of minor updates for STROBE.

Stage 1: PS Model Building

Stage 1 consists of covariate selection, PS estimation, checking overlap, first balance control subtitles. These are defined as follows, respectively.

Covariate Selection

The PS model uses treatment status rather than clinical outcome state as the dependent variable. There are many debates in the methodology literature regarding which variables to include in the PS model. Possible sets of variables that can be included in the PS model are baseline covariates, treatment-related covariates, outcome-related covariates, and both treatment and outcome-related covariates (The concept of "related"; Statistical significance in the literature; clinical significance; or statistical significance as determined by hypothesis tests performed on the data obtained in the current study).

Austin et al. (2007) highlight that excluding the confounding variable(s) in the PS model resulted in biased estimation of the treatment effect [7]. The same study also states that neglect to include a confounding variable in the PS model may lead

to biased estimation of the treatment effect. In addition, this study concludes, variables related to treatment but not related to outcome should not be included in the PS model, because they will not have an improving effect on the results obtained from the PS analysis [5,7]. Brookhart et al. (2006) have suggested that variables not related to treatment but related to outcome should always be included in the PS model, since this reduces the variance of the estimated treatment effect without increasing the bias [19]. In general, it is emphasized that, including the prognostically important covariates (that are outcome-related) or confounding variables (that are treatment and outcome-related) in the PS model should be preferred.

PS Estimation

The stage following the selection of the covariates is estimating the PSs for each participant in the sample. The estimated PS is the predicted probability of treatment obtained from the fitted model. In the case of a categorical treatment (e.g. A-drug vs B-drug), the primary parametric method used in PS estimation is logistic regression. The generalized boosted model (GBM), a nonparametric method proposed by McCaffrey (2004), which automatically includes all higher order and interaction terms of covariates and does not require full data, is frequently used for PS estimation in addition to logistic regression. Besides these methods, various parametric (e.g. probit regression, discriminant analysis) and nonparametric (e.g. tree-based methods, neural networks) methods are used in PS estimation in the literature [8,18,20,21].

Checking Overlap

The next stage after PS estimation is the evaluation of the overlap (also referred to as "common support" in some studies) of PS between treatment groups. How much the PSs overlap between treatment groups is a main issue facing investigators using PS. The similarity of PS distribution among the treatment groups can be evaluated with the Q-Q plot, box-whisker plot, etc. A large overlap increases the confidence that the estimated treatment effect will be generalized to the entire population represented by the sample. On the other hand, a low overlap implies that the treatment effect will only be represented by a small subgroup of the population. The lack of overlap in PSs can be an indication of large differences between treatment groups. In such a situation, unbiased treatment effects cannot be obtained by comparing treatment groups [13].

First Balance Control

Balance and bias have been shown to be related in a simulation study conducted by Belitser et al. (2011). In this study; standardized difference, Kolmogorov-Smirnov distance and Lévy distance showed high correlation with bias [22].

Balance in PS analysis is generally assessed by examining the differences in distributions of covariates between treatment groups [23]. Performing the first balance control in Phase 1 is important to determine the existence, and if exists the degree, of imbalance on covariates. The statistical methods frequently used to assess balance in PS analysis are summarized in Table 2. These should be applied separately for each covariate.

Phase 1 is completed with the first balance control. Next phase consists of two stages, and includes application of the PS methods and treatment effect estimation. These are respectively defined in the following sections.

Stage 2: Application of PS Methods

Stage 2 consists of specifying treatment effect, identifying the PS method to implement, and second balance control.

Specifying Treatment Effect

Treatment effect can be defined as the effect of the treatment arm on the dependent variable or response variable of interest. Average treatment effect on treated (ATT) is the average treatment effect for participants who actually received the treatment, while average treatment effect (ATE) is the average treatment effect for entire participants in the treatment and control groups. If the treatment groups are similar, ATE and ATT give nearly the same results. For this reason, in a RCT, the ATT and ATE are equivalent. Researchers should determine the type of treatment effect (ATE or ATT) in accordance with the purpose of the study. For instance, if countries' approach paths to an epidemic alert are examined, it will be more critical to evaluate the average effect on individuals suffering from pandemics rather than on all individuals [8,13,18].

PS Methods

A vital issue when using PS is to choose the type of PS method to implement. Four different methods are in use: the PS matching, stratification (or subclassification), weighting, and covariate adjustment. A brief summary of the first three methods which are suitable to be schematized is given in Figure 1.

Table 2. Summary of statistical methods used for assessing balance in PS analysis

Balance diagnostic	Short Definition and Interpretation
Variance ratio	It is the ratio of covariate variances between treatment groups. Close to 1 indicates good balance in covariate, while less than 0.5 or greater than 2 indicates extreme imbalance.
Standardized difference	It is the most frequently used balance criterion in the literature and is defined as the absolute treatment group difference in means/rates divided by the pooled standard deviation of the covariate. Although there is no universally accepted threshold to be used for standardized difference, a value of < 0.1 indicates a good balance on the covariates. For a continuous covariate: $d = \frac{(\bar{x}_t - \bar{x}_c)}{\sqrt{\frac{s_t^2 + s_c^2}{2}}}$ $\bar{x}_t$ and $\bar{x}_c$ denoted the sample mean of the covariate in treatment and control groups, respectively. s_t^2 and s_c^2 denoted the sample variance of the covariate in treatment and control groups, respectively. For a dichotomous covariate: $d = \frac{(\hat{p}_t - \hat{p}_c)}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t) + \hat{p}_c(1-\hat{p}_c)}{2}}}$ $\hat{p}_t$ and $\hat{p}_c$ denoted the prevalence of the covariate in treatment and control groups, respectively (Austin et al., 2007; Deb et al., 2016; Austin, 2008; Alam et al., 2019).
Overlapping Coefficient	It measures the amount of overlap of the covariate in the treatment groups. It takes a value between 0 and 1 (0: non-overlap, 1: perfect overlap).
Kolmogorov–Smirnov distance	It is the maximum vertical distance between two cumulative distribution functions of a covariate. It takes a value between 0 and 1 (0: perfect overlap, 1: non-overlap).
Lévy distance	It can be considered as a type of Kolmogorov-Smirnov distance that takes into account both the horizontal and vertical distance between the two cumulative distribution functions. It takes a value between 0 and 1 (0: perfect overlap, 1: non-overlap).

Notes: (1) The statistical methods are defined under the assumption that there are 2 treatment groups. (2) Detailed information on Overlapping Coefficient, Kolmogorov– Smirnov distance and Lévy distance is available in Belitser et al.(2011).

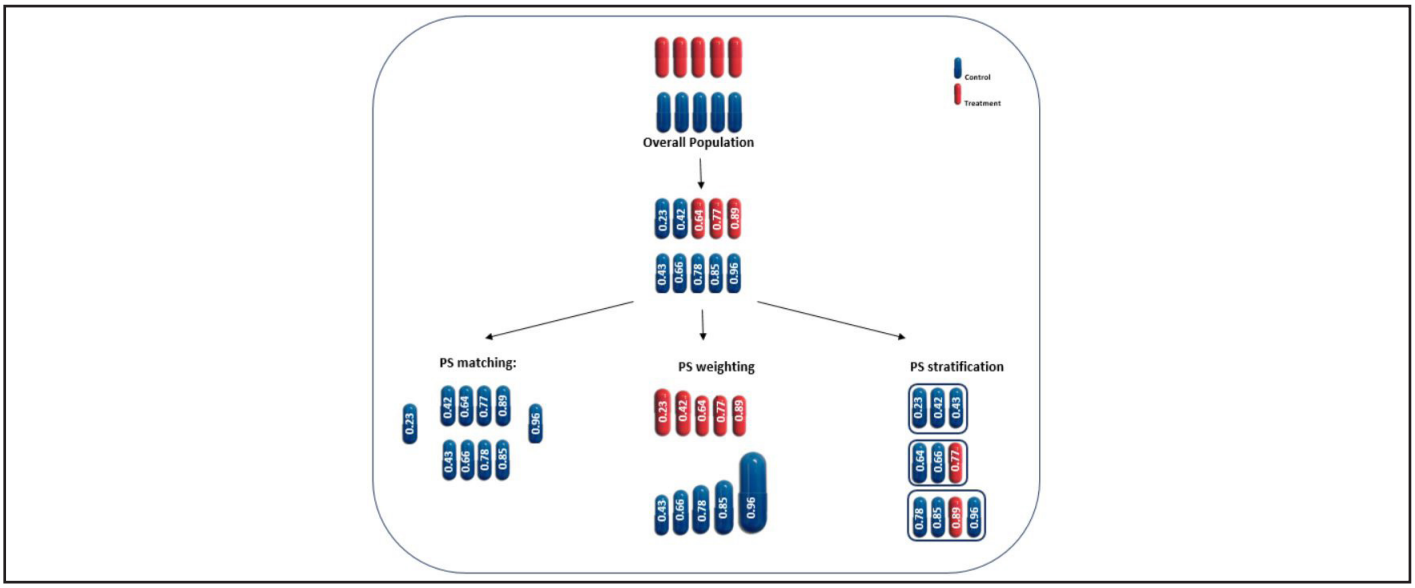

Figure 1. PS methods: matching, weighting and stratification

The overall population is a group of patients, consisting of the treatment group (red) and the control group (blue). Using the PS model, the estimated propensity scores for each patient are given in the figurations. Matching, weighting and stratification were used as PS methods. *PS matching*: In the treatment and control groups, patients with the closest PS values were matched and two patients who could not be matched were excluded. *PS weighting*: The patients were weighted according to their PS and the figurations were scaled according to these weights. *PS Stratification:* Three strata were created considering the closeness of the patients' PS.

PS Matching

PS matching, which makes it possible to obtain ATT estimates, is mainly used to create treatment groups more similar in terms of their distinctive characteristics. In this framework, participants with similar PSs in the treatment groups are matched with the preferred PS matching method. This means a participant in treatment group and participant in control group are matched when the smallest distance between their PSs is obtained. Several PS matching mechanisms are available in the literature. This study will emphasize the most frequently encountered four matching methods in medical literature; namely greedy matching, nearest neighbor matching, optimal matching and full matching will be discussed. In addition to these, there are mechanisms such as kernel matching, genetic matching, difference-in-differences matching etc. to be used as alternatives. For the ease of explanation, it will be assumed that there are 2 treatment groups (treatment and control).

Greedy Matching: The logic of this mechanism is based on matching a participant in the treatment group with the first participant who obtained the closest distance from participants randomly selected in the control group [24].

Nearest Neighbor Matching: This mechanism matches a participant in the treatment group with the participant who obtained the closest distance from many participants in the control group. Greedy and nearest neighbor matching are explained as similar methods under one title in some sources but some authors claim that this may cause confusion among researchers [13].

Optimal Matching: This mechanism is based on minimizing average absolute PS distance called global PS distance in whole matched pairs [24].

Full Matching: The matches are obtained in a similar manner to an optimal matching but the weights are used after matching is performed. In this context, each treated participant is given 1 as weight; and the control participant in each match takes the weight obtained by proportioning the number of participants receiving treatment in the match to the number of control participants in the same match [13].

A disadvantage related to PS matching is that among the discussed matching mechanisms only full matching guarantees all participants to be included in the matching process. It is clear that the exclusion of non-matched participants from the study will result in a decrease in statistical power and loss of both generalizability and precision of treatment effect estimates [15,25].

One point to be considered in the PS matching methods is whether the matching will be made "with replacement" or "without replacement". If a participant in the treatment group is matched with a participant in control group, and that control participant is used again (i.e. matching is done with replacement) a control participant can match with more than one participant in treatment group. Matching with replacement is particularly useful when there are few control participants that can be matched to treated participants. On the other hand, if a participant in the treatment group matches a participant in control group and that control participant is not used again (i.e. matching is done without replacement) precision will be increased but also bias will also increase [16,17,26]. Another point to be considered in PS matching methods is the ratio of treatment and control participants in the matching process. The most common ratio in the literature is 1:1, i.e. matching 1 treatment participant with 1 control participant. Other ratios can also be used (1:M matching) [17].

The restriction of "maximal acceptable difference" was proposed as a solution to the problem of matching individuals whose PSs are not close in treatment groups. Maximal acceptable difference is also called 'caliper' or 'tolerance' and is expressed by ε. Basically, using the caliper means that the closest match is determined by the $d(i,j) < \varepsilon$ inequality, where and j represent the individuals in the treatment and control groups respectively. The caliper proposed by Cochran and Rubin (1973) is $\varepsilon < 0.25\sigma_{ps}$, σ_{ps} being the standard deviation of PS [3]. Another approach is matching participants using calipers of width equal to 0.2 of the standard deviation of the logit of PS [17,24]. Austin (2011) states

that the usage of this stated approach eliminates about 99% of the bias and minimizes the mean square error of the treatment effect. In some studies, however, the restriction of maximal acceptable difference is considered as a separate matching method (namely caliper or radius matching) [6].

PS Stratification

In the PS stratification method (which is also known as the PS subclassification method), the PSs of the participants are ordered and using these PSs, mutually independent stratas of approximately equal sizes are created. Commonly, it is recommended to use 5 strata, which are formed by quintiles of ordered PSs, because this causes about 90% reduction in bias [4,9,14]. It has also been suggested that it is appropriate to use 10 or 20 strata if the sample size is large [16].

PS Weighting

In the PS weighting method, the treatment and control participants in the sample are weighted with the weights produced from their PSs. Both ATE and ATT estimates can be obtained in PS weighting, although with different mechanisms. In this context, ATT estimation is produced using 'weighting by the odds', and ATE estimation using inverse probability weighting.

Weighting by the Odds: In this mechanism, every participant in the treatment group receives a weight of 1, while participants in the control group receive a weight of their PS, converted to the odds scale ($e_i / (1-e_i)$). With weighting by the odds, the control participant whose PS is closer to the participant in the treatment group receives more weight [27].

***Weighting by Inverse Probability of Treatment Weights (IPTW*)**: The difference of this mechanism from weighting by the odds is that the participants in the treatment group also receive weights based on PS. In IPTW, each participant is weighted by the inverse probability of receiving the treatment. In this case, the participant in the treatment group is weighted with $1/e_i$ and the participant in the control group with $1/(1-e_i)$. A problem that may arise in IPTW is that a participant in the treatment group with a very low PS receives a very large weight, or similarly, a participant in the control group with a PS close to 1 receives a very large weight. It is not recommended to simply exclude these participants from the study, instead some approaches have been proposed to deal with extreme weights. One of the approaches, the stabilization procedure, uses the standardized weights $\hat{e}/e_i$ for the treatment group and $(1-e)/1-e_i$ for the control group where $\hat{e}=1 / \sum_{i=1}^{n} e_i$). Another approach is the trimming procedure that restricts all participant weights to a predetermined range. In the literature, the trimming is often applied to the extreme 1% or 5% of the weights [15,28]. Detailed information on trimming procedures is availabled in the study by Yoshida L. et al(2019) [29].

PS Covariate Adjustment

In this PS method, PSs produced in the Stage 1 are included in the treatment effect model as explanatory variables. In other words, PS is used as a control variable in estimating the treatment effect. An important assumption in this method is that the nature of the relationship between PS and the outcome is modeled properly [8,17,18].

Second Balance Control

Once the PS methods are implemented, the next stage is mainly evaluating whether the PS model has been adequately specified. The adequacy of the PS model, in other words, the success of the PS model can be evaluated by comparing the balance between treatment groups [8,18]. The statistical methods in Table 2 can also be used in this stage, with slight differences. For PS matching, the calculations are made considering the matching samples whereas for PS weighting, the weighted sample should be taken into consideration. For stratification, the calculations are made separately for each strata [8,18]. Besides the five statistical methods summarized in Table 2, statistical significance tests, Hosmer-Lemeshow goodness of fit test and c-statistic are also used for balance assessment [30]. The quality of a PS model must be evaluated on the basis of how well individual characteristics are balanced between the two treatment groups. For this very reason, a number of studies declare that goodness of fit tests such as the Hosmer-Lemeshow test or discriminant measures such as c-statistics are not suitable for balance assessment [5,17,19,31]. A detailed information on why statistical significance tests should not be recommended for balance assessment can be found in Austin (2011) [8,18].

It should be noted that, the difference between the treatment groups in terms of the covariate of interest (i.e. imbalance) at this stage may be due to the incorrect specification of the PS model or the use of an inappropriate PS method [17]

Graphical methods such as Q-Q plots, cumulative distribution functions, side-by-side boxplots and density plots can also be used in balance assessment for continuous covariates [8,18]. In

the mostly encountered Q-Q plot, the distribution of a covariate in the treatment group is plotted against the distribution in the comparison group and the covariate is considered balanced if a 45 degree straight line is obtained [32].

Stage 3: Treatment Effect Estimation

After the second balance control has been conducted, the next step is the treatment effect estimation. At this stage, general or generalized linear models can be used for any PS method. The type of outcome variable determines which modeling approach will be used. For instance, the linear regression model can be used in the case of a continuous outcome variable (e.g. hemoglobin), and the logistic regression model in the case of a binary outcome variable (e.g. mortality).

Different PS methods require different treatment effect estimation models. In the PS matching method, treatment effect model is fitted to the matched sample. In the PS stratification method, treatment effect model is fitted separately within each strata and the treatment effects obtained from the fitted models for each strata are pooled to calculate an overall treatment effect estimate [15,17]. In the PS weighting method the calculated weights have to be included in the treatment effect model as a weighting variable.

At the end of Stage 3, it is recommended that researchers perform a sensitivity analysis in which they explore to what extent the estimated treatment effects are robust to hidden bias [16].

Table 3. Quality Checklist of PS Analysis

	Item	✓ or X
Preparation for PS Analysis		
	1. Point out the scientific background	☐
	2. Indicate key components of study design	☐
	3. Clearly state the objective(s) of the study	☐
	4. Describe data sources and measurement methods for all variable of interest	☐
PS Model Building		
	5. Determine the appropriate set of variables to use in the PS model	☐
	6. Decide the PS estimation method (parametric and nonparametric) and explain why select to this method	☐
	7. Evaluate the overlap and state the method(s) used for checking overlap	☐
	8. Present the degree of first balance and state balance diagnostic(s) used	☐
Application of PS Methods		
	9. Specify the type of treatment effect	☐
	10. Explain which PS method is used a) If weighting or matching is used, state which strategy were chosen b) PS weighting method - state how to deal with extreme weights, if any c) PS matching method - state the ratio of treatment and control, indicate if there are any excluded participant(s), specify whether matching was done with or without replacement, report caliper if used d) PS stratification method - state how many strata are used	☐
	11. Present the degree of second balance and state balance diagnostic(s) used	☐
	12. State which model approach is used for treatment effect estimation	☐
	13. Perform the Sensitivity analysis	☐
	14. Report and interpretation of treatment effect	☐

PS: Propensity Score

Stages of PS analysis can be applied with many statistical software such as R, Stata, SAS. A detailed implementation of the PS stages in STATA and SAS are available in Lunt(2014) and Lanehart(2012), respectively [33,34]. Which program is preferred depends on which software the researcher is comfortable with.

RESULTS AND DISCUSSION

In recent decades, the use of PS analysis in clinical studies has increased dramatically. It can be said that the PS analysis performed do not fit a standard pattern in many of these studies. With the aim of standardizing the steps in PS analysis, a basic guideline has been presented. In addition, a checklist in parallel with the guideline that can be easily used by researchers to standardize PS analysis is included in the Table 3. From the planning stage of the PS analysis, this checklist offers researchers the opportunity to control their step-by-step implementation as well as making it possible for them to make an assessment on the quality of their PS analysis. We believe that the quality of future PS analysis will increase if such checklists are followed. Since the use of PS analysis methods are being more and more frequent, we propose that the integration of the crucial steps into STROBE (the Strengthening the Reporting of Observational Studies in Epidemiology) Statement may also be taken into consideration. To be concise, items in the "Participants, Bias and Statistical Methods" sections of STROBE can be updated to question, and explain the efforts to overcome selection bias by using PS analysis methods [35].

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Case Report

An Old Complication Welcomes Us in the Modern Era: Lingual Hematoma During Thrombolytic Therapy

Sevda Aygün[1], Uğur Canpolat[1]

[1] Hacettepe University Faculty of Medicine, Department of Cardiology, Ankara, Turkey

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Correspondence
Uğur Canpolat, MD,
Address: Hacettepe University Faculty of Medicine, Department of Cardiology, 06100, Sıhhiye, Ankara/Turkey
Email: dru_canpolat@yahoo.com

ABSTRACT
Lingual hematoma is a rare but potentially life-threatening clinical condition. Securing the airway and urgent treatment for underlying reasons are key management steps. We reported a case to illustrate the management of a lingual hematoma after rescue thrombolysis for a ST-segment elevation myocardial infarction (STEMI) patient.

Keywords: lingual hematoma, rescue thrombolysis, complication

INTRODUCTION

Thrombolytic therapy is not a priority in the modern era of ST-segment elevation myocardial infarction (STEMI) treatment and primary percutaneous coronary intervention (PCI). In the late 1990s, studies demonstrated that PCI is associated with lower mortality and complications and is superior to thrombolytic therapy [1]. Alteplase (tPA) is the most commonly used thrombolytic agent and requires close monitoring and regular physical examinations during treatment for early detection of complications. Due to the non-selective lytic activity of tPA, the lytic state occurs, which can manifest as bleeding in various organs [2].

Lingual hematoma is a rare entity, but multiple cases have been reported about various causes of lingual hematoma. Trauma, vascular anomaly, or coagulation disorders come forward as the three main causes [3-5]. According to pathophysiology, different treatment modalities are used, such as surgery or angiographic embolization of the lingual artery for traumatic hematomas and discontinuation and reversal of anticoagulants for coagulation problems [6]. Although it's rare, it is important to distinguish because of its rapidly progressive nature. Airway management and mantainence of sufficient passage could be troublesome and urgent advanced assistance can be required [7]. Herein, we reported a patient with STEMI in whom lingual hematoma has been developed during rescue thrombolytic infusion.

We obtained both verbal and written informed consent from the patient for the submission of this manuscript.

CASE

An 80-year-old male patient presented to the emergency department (ED) with chest pain that radiated from the left arm. ECG was performed on arrival and showed inferoposterolateral STEMI. The heart rate was between 56 and 72 bpm, and blood pressure was 93/61 mmHg. The results of serum blood chemistry studies, blood cell counts, and other coagulation studies were within the respective normal limits. Aspirin (300 mg),

clopidogrel (600 mg), atorvastatin (80 mg), and unfractionated heparin (UFH) (4000 IU intravenous bolus) were administered at the ED. The patient was transferred for emergent coronary angiography, but a failure occurred while the guidewire entered the distal lumen. An additional 1000 IU intravenous UFH (a total of 70 IU/kg) has been administered before percutaneous coronary intervention. Then, it is decided to give a fibrinolytic agent to achieve myocardial perfusion. After the admission of the patient to our coronary intensive care unit (CCU), a bolus of recombinant tPA was administered (15 mg) in 1 minute, and infusion was started (50 mg over 30 minutes and 35 mg over 1 hour). The UFH infusion rate was decreased at 500 IU/h while tPA was administered. Several ECGs were taken for monitoring ST-segment resolution and myocardial reperfusion. After thrombolytic therapy, the patient complained of glossal swelling and difficulty in speech within 45 minutes. There had been no trauma or instrumentation in the mouth. Physical examination revealed significant swelling and purple-black discolourization of the tongue (Figure 1). There was no dyspnea, stridor, or neurological symptom additionally. He has been consulted to the otorhinolaryngology (ENT) department and a fiber optic transnasal endoscopic examination was performed. On exam, no interruption of the airway was detected and due to enough passage of the upper airway, intubation or tracheostomy were not required. Lingual hematoma due to thrombolysis and anticoagulation therapy was considered as the initial diagnosis. Infusion of UFH was stopped, and protamine was administered for the reversal of anticoagulant effect of UFH. The repeated physical examinations revealed that lingual hematoma was completely resolved spontaneously (Figure 2). The patient did not have any other complaints during the in-patient follow-up. During observation and treatment for acute coronary syndrome, acute kidney injury was observed, and the patient has transferred to another in-patient clinic of the internal medicine department.

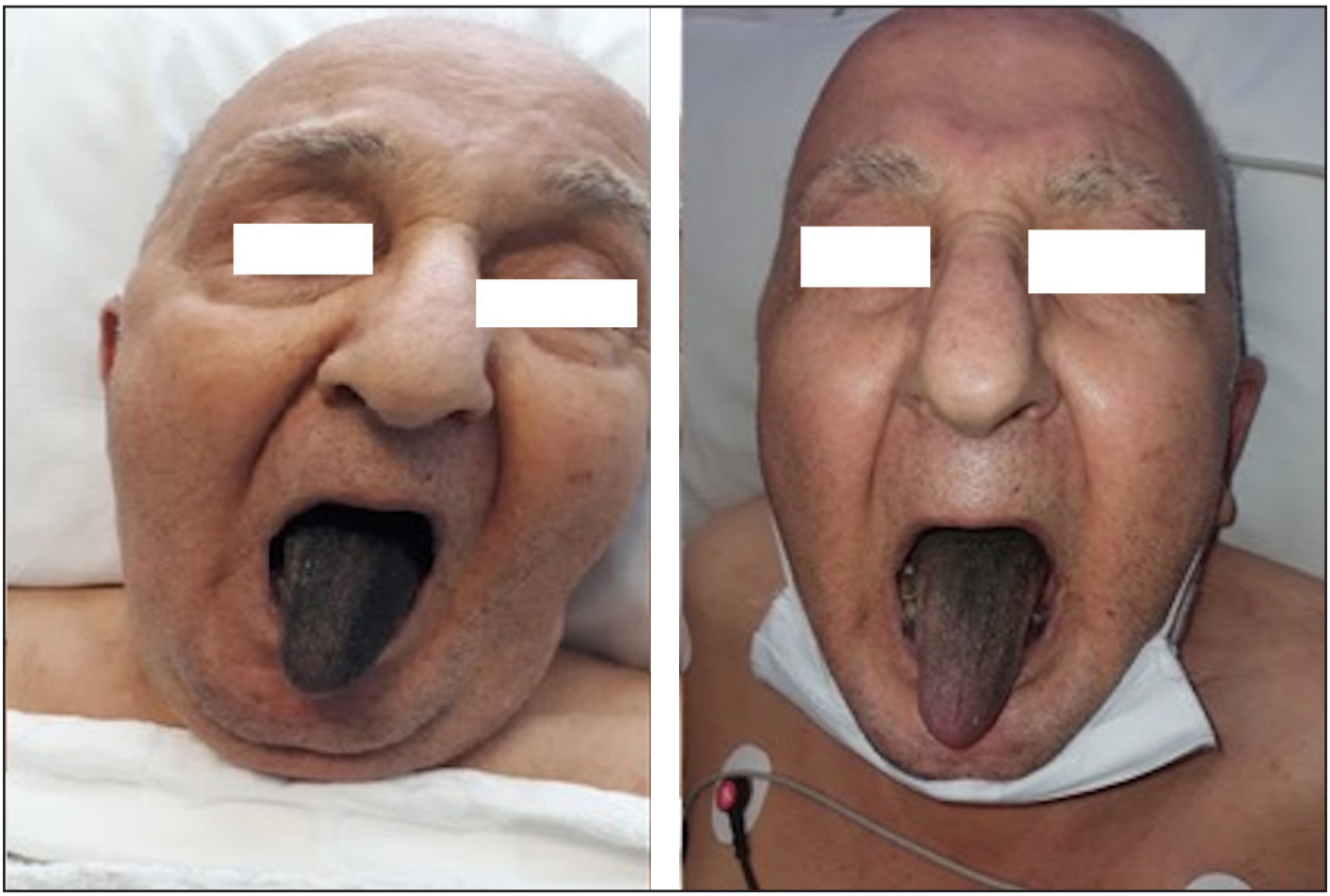

Figure 1. View of the lingual hematoma during alteplase (t-PA) infusion.

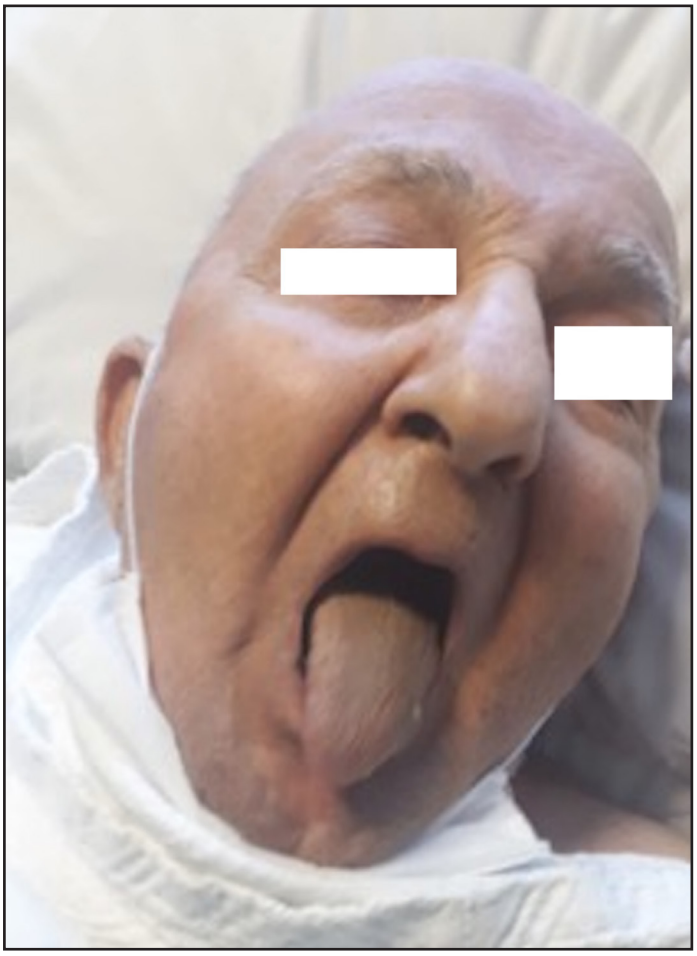

Figure 2. Spontaneous resolution of hematoma and normal appearance of the tongue after discontinuation of tPA and heparin infusion.

DISCUSSION

Fibrinolytic therapy is often used as a first-line treatment for STEMI when PCI is not available, but it can also be used as a rescue treatment in patients who have undergone unsuccessful PCI, just as in our case [8]. It is important to note that the use of fibrinolytic therapy to treat STEMI can increase the risk of bleeding complications, including lingual hematoma. Peri-procedural use of UFH (both during primary PCI and tPA infusion) may also increase the risk of bleeding because of additive anticoagulant effect. Therefore, patients receiving fibrinolytic therapy should be closely monitored for signs of bleeding, and the medical team should be notified immediately if any bleeding complications occur. The risk of bleeding can be minimized by ensuring that patients are appropriately selected for fibrinolytic therapy based on their clinical characteristics and by using appropriate dosages of fibrinolytic agents [9]. Furthermore, the dosage of the UFH should be modified according to the bleeding risk of the patients appropriately and reversed in case of life-threatening bleeding complications.

Lingual hematoma is an infrequent but potentially serious complication that can occur after fibrinolytic therapy for STEMI. The severity of the hematoma can vary depending on the size and location of the hematoma and the patient's overall health status. The management of lingual hematoma after fibrinolytic therapy for STEMI requires a multidisciplinary approach. The first step in the management of lingual hematoma is to ensure that the patient's airway is secure, as large hematomas can cause airway obstruction and respiratory distress [10]. The medical team should closely monitor the patient's vital signs and oxygen saturation levels to ensure that they are stable. In cases where the hematoma is small and not causing any significant symptoms, the medical team may choose to observe the patient closely and monitor the hematoma's progression. Larger hematomas that cause airway obstruction may require surgical intervention. The surgical approach may involve draining the hematoma by making an incision in the floor of the mouth. This procedure is typically performed under local anesthesia, and the patient should be consulted by an ENT specialist in case of surgical intervention. Another approach to airway management in lingual hematoma is to perform a tracheostomy [11]. While this is an effective method of securing the airway in cases of severe obstruction, it is an invasive procedure and carries a risk of complications.

In this case, we preferred thrombolytic therapy after ineffective PCI as a rescue approach for myocardial perfusion. Although lingual hematoma is a rare complication of tPA therapy, clinical condition varies according to the severity of airway obstruction and requires prompt recognition and management. A multidisciplinary approach is necessary to ensure the best possible outcomes for patients. In our case, after the cessation of therapy, a regression was detected and no further approach was performed.

In conclusion, our case report illustrates the importance of the management of lingual hematoma and underlines that physicians should also be vigilant for signs of bleeding complications associated with fibrinolytic therapy and take appropriate steps to minimize the risk of these complications.

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Case Report

Cryptococcal Meningitis in a Human Immunodeficiency Virus Sero-positive Patient – A Case Study

Jayalakshmi Srinivasan[1], Neha Singh[1], Nidhi Anam[2], Snehal Wagh[1], Shubhangi Sharma[1]

[1] Department of Microbiology, MGM Medical College, Navi Mumbai
[2] Department of Medicine, MGM Medical College, Navi Mumbai

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Correspondence
Dr. Neha Singh, Assistant Professor, **Address:** Department of Microbiology, MGM Medical College, Navi Mumbai.
E-mail: drnehasingh4@gmail.com

ABSTRACT

A 42-year-old female patient was admitted to the hospital with moderate grade fever, severe headache, loss of appetite and sore throat. She was suspected for Meningitis and her CSF sample was sent to the Laboratory for Microbiological Examination. The CSF sample obtained showed the presence of capsulated budding yeast cells on India Ink Examination and Cryptococcus neoformans was isolated on sabroud's dextrose agar (SDA) culture. The patient was recently diagnosed as HIV-Sero Positive and was immunocompromised leading to acquiring of Cryptococcal meningitis. The lack of awareness of human immunodeficiency virus infection-acquired immune deficiency syndrome (HIV-AIDS) and delayed diagnosis of Cryptococcal meningitis led to the poor prognosis. Early diagnosis of HIV and timely treatment can improve the prognosis of the disease.

Keywords: cryptococcal meningitis, human immunodeficiency virus, cerebrospinal fluid, central nervous system, gram staining.

INTRODUCTION

Cryptococcus neoformans, so far is the most common cause of Cryptococcal meningitis in adults with high human immunodeficiency virus infection (HIV) seroprevalence. The prevalence is higher in Sub Saharan Africa despite of having improved retroviral therapies. Also, prevalence of Cryptococcal meningitis in non-HIV patients is a matter of concern [1]. In India, it is the most common opportunistic infection of central nervous system (CNS) in HIV Patients. HIV patients having CD4 count less than 100 cells/µl are usually affected with Cryptococcal meningitis [2].

Diagnostic procedures include examination of cerebrospinal fluid (CSF) wet mount, India Ink, Cryptococcal antigen tests and culture methods [3]. With limitations in therapies with antifungal drugs due to raised intracranial pressure, Amphotericin B along with flucytosine is the drug of choice for two weeks followed by Fluconazole for another 8 weeks. Here, we report a case of Cryptococcal meningitis in patient with positive Retroviral Disease due to low immune status [4].

CASE REPORT

A 42-year-old female patient, recently diagnosed with retroviral disease was brought to outpatient department on January 21, 2022. She was apparently well 20 days back but suddenly developed moderate grade fever with chills which were relieved with simple medication. 10 days later she had a complain of

severe headache (Holocranial - more in occipital area extending till neck). She also complained of sore throat and loss of appetite. There was no history of nausea, vomiting, cough, breathlessness, palpation, dizziness, involuntary movement, or loss of consciousness. Examination showed poor G and C bases of deoxyribonucleic acid (DNA), pulse rate 74 mm Hg, blood pressure of 160/90 mm Hg, SpO_2: 98% on room air and random blood sugar (RBS) was 216 mg/dl. On admission, neck rigidity was positive.

The patient was admitted to medical intensive care unit (MICU0 and CSF sample was sent to microbiology laboratory. Wet mount, India Ink, Gram staining, and culture was performed immediately for the CSF samples as per standard procedures.

Wet mount examination revealed, 2-4 pus cells/ hpf, > 15 red blood cells (RBCs)/ hpf and 0-1 Epithelial cell/ hpf. India Ink examination revealed, few capsulated budding yeast cells with diameter 4-7 µm (Figure 1). Gram staining examination revealed, few pus cells were seen and few budding yeast cells (Figure 2). On sabroud's dextrose agar, CSF was cultures by standard microbiological procedures. After 48 hours of incubation, Creamy white mucoid colonies were observed (Figure 3). The wet mount, Gram stain, and India Ink preparation from the growth revealed capsulated budding yeast cells (Figure 4). The organism was further confirmed by brownish color colonies on bird seed agar and by a positive urease test (Figure 5 and Figure 6). Hence according to the microscopic and culture findings, the organism isolated was Cryptococcus neoformans.

Also, on correlating with CSF routine and microscopy, the CSF protein levels were increased to 128.28 mg/dl and CSF glucose levels were decreased to 39.7 mg/dl. Correlating the clinical symptoms and the microscopic and culture finding, the diagnosis of Cryptococcal meningitis was confirmed.

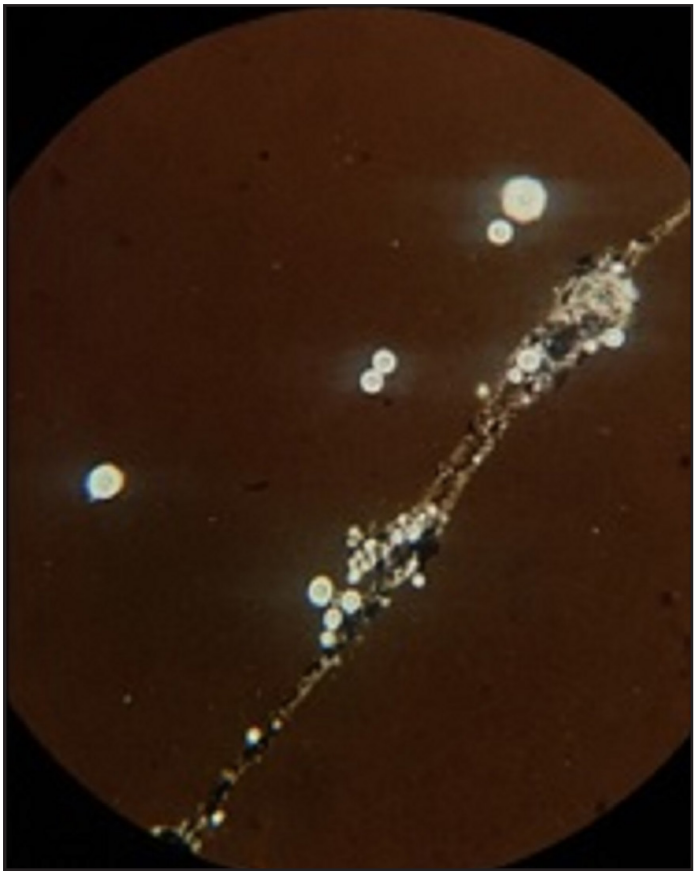

Figure 1. CSF sample showing capsulated budding yeast cells in India Ink

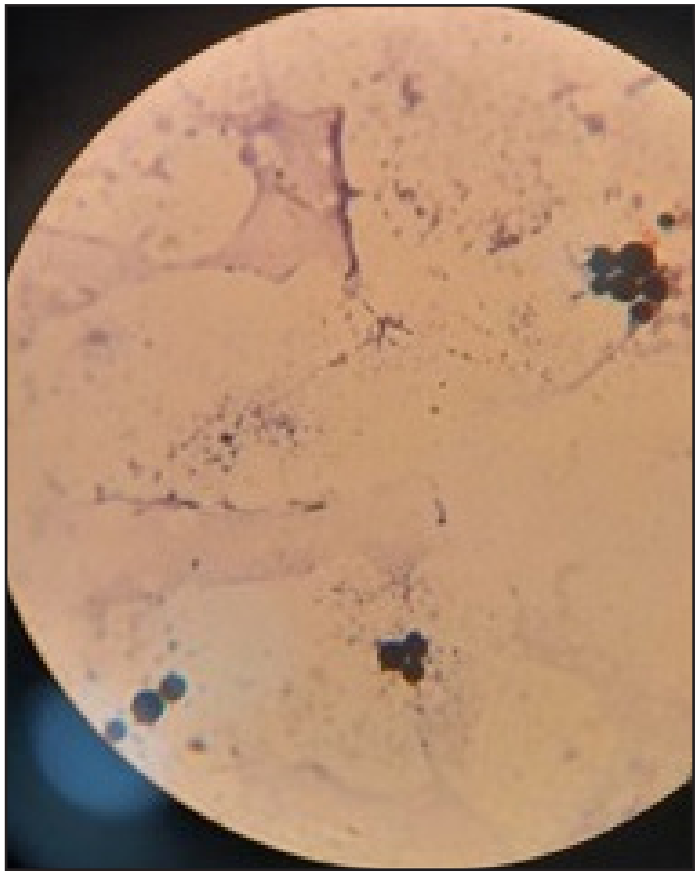

Figure 2. CSF sample showing budding yeast cells in gram staining

Figure 3. Creamy white mucoid colonies on sabroud's dextrose agar

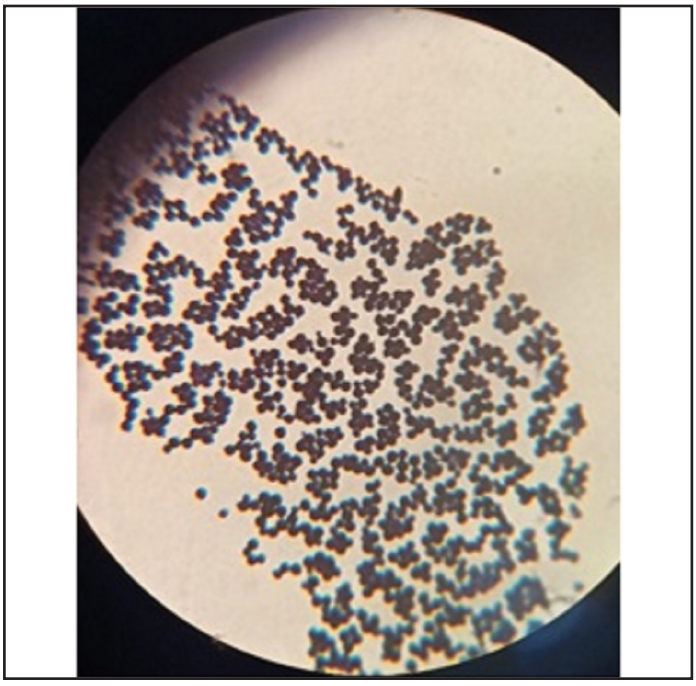

Figure 4. Gram staining showing budding yeast cells of colonies grown on sabroud's dextrose agar

Figure 5. Bird seed agar showing brown colored colonies

Figure 6. Positeive urease test

DISCUSSION

Cryptococcal meningitis is one of the most common opportunistic infections associated with human immunodeficiency virus infection-acquired immune deficiency syndrome (HIV-AIDS). It is the leading cause of death with a mortality rate of 7-15% in HIV Patients around the world. The major reason behind the high mortality rate is mis-diagnosis due to late presentation of disease, serious complications and lack of awareness about HIV-AIDS and its associated opportunistic infections [5-7].

In this case study, the patient was recently diagnosed with HIV disease which indicates that her CD_4-CD_8 count was lower making her prone to the opportunistic infections. The patient was admitted in the MICU and she was treated with Injection Ceftriaxone 2 gm and her CSF sample was sent for microbiological examination but before her diagnosis of Cryptococcal meningitis could be made, she collapsed as appropriate antifungal therapy could not be started on time.

To treat this deadly disease, antifungal agents like Flucytosine and Liposomal Amphotericin B are used although they have poor CNS penetration effect. These medications are quite expensive and cannot be afforded by the poor families like this patient. Hence instead of Flucytosine, consolidation therapy consisting of Fluconazole 400-800 mg/day can be administrated. To check the prognosis of disease, the CSF sample should be tested again in 2 weeks after the start of therapy as Flucytosine is a fungistatic medication [6,8].

The antifungal doses should be reduced with the prognosis of disease as to avoid the resistance towards these antifungal agents as reduced susceptibility towards these antifungal agents have also been documented. Also, in HIV Sero positive patients, these antifungal therapies should be started in combination with Anti-retroviral therapy so as to prevent opportunistic infections in patients with CD_4 count less than 200 cells/ml [9-11].

CONCLUSION

Cryptococcus are majorly found in soil contaminated with excreta of birds particularly pigeons. The humans are infected by inhaling the contaminated aerosols with Cryptococcus. This patient worked as a laborer at a construction site which could be a major reason for her to acquire Cryptococcal meningitis as she was already an immuno compromised patient. Cryptococcus is the most common fungal pathogen in AIDS patients as it can lead to increased mortality if not treated immediately.

Hence, studies on spectrum and prevalence of prevalence of opportunistic infections should be done regularly to create awareness towards HIV and its co-infections among clinicians as well as among patients as in the case of this patient who was recently diagnosed with HIV and was not aware about the opportunistic infection leading to untimely diagnosis, treatment and ultimately death.

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Conflict of Interest: The authors do not have any competing interests.

Author's Contribution: The final manuscript was reviewed and approved by all authors.

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Letter to Editor

The Rising Tide of Artificial Intelligence in Scientific Journals: A Profound Shift in Research Landscape

Ricardo Grillo [1,2]

[1] Department of Oral and Maxillofacial Surgery, Traumatology and Prosthesis, Faculty of Dentistry of the University of São Paulo, Brazil
[2] Department of Oral and Maxillofacial Surgery, Faculdade Patos de Minas, Brasília, Brazil

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Correspondence
Ricardo Grillo, DDS, MSc
Address: University of São Paulo
Faculdade de Odontologia
Av. Prof. Lineu Prestes, 2227.
Cidade Universitária,
São Paulo-SP-Brazil. 05508-000
E-mail: doutorgrillo@uol.com.br

Dear Editors,

I found the content of your editorials to be highly intriguing [1,2]. Scientific journals are witnessing a growing prevalence of publications related to artificial intelligence (AI). Three letters to the editor were recently published in your journal [3-5]. The renowned journal Nature has dedicated approximately 25 publications solely to the subject of ChatGPT. Moreover, a quick search on Pubmed using the term "ChatGPT" yields around 900 articles, with the vast majority originating in 2023. These statistics underscore the substantial interest of the scientific community in this area.

AI, especially the ChatGPT tool and the recent Bard, have faced criticism and been portrayed as significant adversaries of science. It is evident that many authors or researchers, who may not be well-versed in writing, can greatly benefit from these tools, as mentioned earlier. Without taking a contrarian stance, one should consider the potential advantages of such technologies for researchers in less privileged regions, where access to new technologies is limited, and local or regional challenges abound [6]. AI cannot be confounded with other technologies, as it specifically focuses on replicating human-like intelligence and decision-making processes, rather than simply automating tasks or improving performance based on data patterns.

The translation into English poses challenges due to the dominance of English in worldwide publications, with over 95% of articles being published in this language, and even reaching 98% in some fields. Although this manuscript was partially translated using AI, it can still benefit researchers from non-native English regions. Even simple tasks like text editing can be problematic for researchers in underprivileged areas. AI can play a crucial role in the evolution of online lectures and classes, providing valuable support for African maxillofacial surgeons who lack the luxury of taking breaks from work to update their knowledge, as they may be the only available option [7]. One of the remarkable features of AI is its ability to discover knowledge gaps. The use of simple tools like reference organizers is rapidly evolving and can become automated or semi-automated through AI. However, we must carefully consider whether we should refrain from relying too heavily on AI in certain cases, as this could be seen

as a significant regression.

On the other hand, we must be cautious about freely allowing AI tools to circulate in scientific journals and books without proper regulation [8]. Currently, accurately identifying texts generated by AI is challenging, and their effectiveness remains relatively low, at less than 30%. This means that only about 30 out of every 100 texts can be confidently classified as AI-generated. The technology must advance further to increase detection accuracy or at least raise suspicion. Academic journals no longer view authors acknowledging artificial intelligence tools as co-authors in their research favorably. This is crucial to prevent certain unscrupulous individuals, such as "false prophets," charlatans, and flat-earthers, from infiltrating the realm of science, potentially impeding the progress of serious research conducted by professionals dedicated to advancing humanity through science.

It is essential to keep in mind that AI does not generate anything novel. Human authors can not be fully substituted [9]. In research involving groundbreaking concepts, innovations, case reports, or technical notes, the use of AI tends to be less frequent due to its lack of capability in creating innovative outcomes. On the other hand, reviews, whether narrative, systematic, or scoping, are based on existing publications. To address potential fraudulent practices, editors, reviewers, and journals themselves should exercise greater vigilance and apply more stringent filters for this type of publication.

An article from over a decade ago already discussed the professions most susceptible to replacement by computerization [10]. Maxillofacial surgeons, physicians, dentists, and psychologists are among the professions that are less likely to be displaced. This position can be attributed to the significant level of patient-professional interaction, the development of specific manual skills over time, and the ability to make adaptable decisions during procedures. These intricacies pose formidable challenges for AI to grasp, regardless of its level of advancement. We should maintain a composed yet vigilant stance at this juncture. Just as Portuguese navigators feared encountering serpents and sea monsters when they ventured into uncharted waters, the uncertainty and novelty of AI can evoke apprehension in us all. Nonetheless, we must embrace the benefits that AI can offer while imposing strict regulations and appropriate penalties to prevent any potential abuses carried out "in the name of science."

Sincerely yours,

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Acknowledgment: None

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