ISSN 2564-7784
EISSN 2564-7040

Indexed in Web of Science

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Formerly Gaziantep Medical Journal

VOLUME 30 ISSUE 3 JUNE 2024

eurjther.com

ISSN 2564-7784
EISSN 2564-7040

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About the Journal

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.

The European Journal of Therapeutics will be published bimonthly, commencing in 2024 (six issues a year in February, April, June, August, October and December).

European Journal of Therapeutics aims to contribute to the international literature by publishing Original Articles, Reviews, Case Reports, Special Editorial, Short Communication, Technical Notes, Letters to the Editor, Reply by Authors, Image, Withdrawn, Erratum, Retraction Notice, Editorial (EIC use only), In memory of (Invited by EIC only) and Book Review (Invited by EIC only) in the fields of medical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.

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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), National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.eurjther.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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E-mail: info@perayayincilik.com
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Printing–Binding
Pınarbaş Matbaacılık Ltd. Şti.
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European Journal of Therapeutics
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Instructions to Authors

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 and its publication language is 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 Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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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The similarity rate limit determined for our journal is 24%.

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

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.

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Manuscript Types

Authors should determine the type of paper before submitting it and indicate the type of paper on the title page. This is because, depending on the type of paper, the rules to be followed, including formatting and word limits, change.The categorization system is at the discretion of the Editor-in-Chief. Authors may be asked to change the article type at the request of the editor at any stage of submission, including after acceptance.
The following types of papers will be considered for publication.

Original Articles: This is the most important type of article since it provides new information based on original research.
Abstracts should not exceed 500 words and should be structured with the following subheadings: Objective, Methods, Results, and Conclusion.
The main text should be structured with the following subheadings: Introduction, Material and Methods, Results, Discussion, Limitations, Conclusions, Acknowledgments, References, Main Points, and Figure Legends.
The main text should not exceed 3000 words, excluding the abstract, references, tables, and figure legends.
There should be a maximum of 50 references.
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).
Please check Table 1 for the limitations for Original Articles.

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.

Case Report: In the European Journal of Therapeutics, very interesting or rare cases can be published as Case Reports. However, due to the limited number of publications determined for this category, it is recommended that you submit such articles as Letter to the Editor. For the instructions for Letter to the Editor, please see below.

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.

Letter to the Editor: The European Journal of Therapeutics encourages authors to write letters to the editor on all topics covered by the journal. There is no abstract requirement for this type of manuscript. If authors prefer to include an abstract in the letter, they may include a short unstructured abstract of no more than 200 words.
It is recommended that a letter contains up to 10 references.
The letter recommends adding "Dear Editor" at the beginning of the main text and "Yours sincerely" at the end.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3000	500 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	200	20	5	1 or total of 5 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images

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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)

These forms are available for download at https://eurjther.com/index.php/home/forms.

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/meshhome.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.

Authors are responsible for the accuracy of references.

References

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

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/.....").

Use abbreviations for journal names. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed.

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

Example for Journal Article without English Titles
Aktan-İkiz A, Üçerler H, Orhan M (2007) Anatomic features of fossa navicularis at the skull base and its clinical importance [Kafa iskeletinde fossa navicularis'in anatomik özellikleri ve klinik önemi]. Sendrom 19:34–36 ([In Turkish])

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

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

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

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.

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.

Corrections, Retractions, and Republications

European Journal of Therapeutics follows and implements the International Committee of Medical Journal Editors (ICMJE) recommendations on Corrections, Retractions, Republications and Version Control.

Corrections, Retractions, Republications and Version Control*

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Matters of debate are best handled as letters to the editor, as print or electronic correspondence, or as posts in a journal-sponsored online forum. Updates of previous publications (e.g., an updated systematic review or clinical guideline) are considered a new publication rather than a version of a previously published article.

If a correction is needed, journals should follow these minimum standards:

- The journal should publish a correction notice as soon as possible detailing changes from and citing the original publication; the correction should be on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing.
- The journal also should post a new article version with details of the changes from the original version and the date(s) on which the changes were made.
- The journal should archive all prior versions of the article. This archive can be either directly accessible to readers or can be made available to the reader on request.
- Previous electronic versions should prominently note that there are more recent versions of the article.
- The citation should be to the most recent version.

Pervasive errors can result from a coding problem or a miscalculation and may result in extensive inaccuracies throughout an article. If such errors do not change the direction or significance of the results, interpretations, and conclusions of the article, a correction should be published that follows the minimum standards noted above.

Errors serious enough to invalidate a paper's results and conclusions may require retraction. However, retraction with republication (also referred to as "replacement") can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then retraction with republication of the changed paper, with an explanation, allows full correction of the scientific literature. In such cases, it is helpful to show the extent of the changes in supplementary material or in an appendix, for complete transparency.

* Corrections, Retractions, Republications and Version Control https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html Date of Access: 05.10.2023

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E-mail: info@eurjther.com

Publishing Service: Pera Publishing Services
Address: Ataköy 3-4-11 Kısım Mah. Dr Remzi Kazancıgil Cd. O-114 N:12 D:7 Bakırköy İstanbul, Türkiye
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pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):e26-e27.
https://doi.org/10.58600/eurjther2252

Editorial

Welcome to the June 2024 Issue (Vol: 30, No: 3) 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], Davut Sinan Kaplan [7], Mehmet Karadağ [8], Ayşe Aysima Özçelik [9], Fatih Sarı [10], Hamit Yıldız [11], Murat Akbaba [12], İlyas Başkonuş [13]

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Published Online: 2024-06-30

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Dear Colleagues,

It is our pleasure to share the valuable articles in a new issue of the *Eur J Ther* (2024; Vol: 30, Issue: 3). We would like to take this opportunity to thank once again the authors who submitted valuable papers to the journal and the referees who evaluated these articles.

In April 2023, we shared that the editorial team of *Eur J Ther* underwent many changes and was updated with a dynamic team [1]. We then made a series of improvements in a short period of time. First, we strengthened our editorial team with many internationally respected academics [2]. In July 2023, Web of Science calculated the journal's impact factor value for the first time as 0.3 [3]. Then, with the dedicated work of the updated editorial team, the journal was soon included in many essential indexes such as Index Copernicus (approved 2023-10-31), ERIH PLUS (approved 2023-06-21), BASE (approved 2023-11-30), and Sherpa Romeo (approved 2023-09-27). As a result of our application, as of the beginning of 2024, articles that have not yet been assigned to the issue and are in early view have started to be indexed in the Web of Science in a short time [4]. This is reflected in the *Times Cited and Publications Over Time* graphic on the Web of Science (Fig. 1) [5]. Another significant development was that from 2024 onwards, the journal will be published six issues a year instead of four.

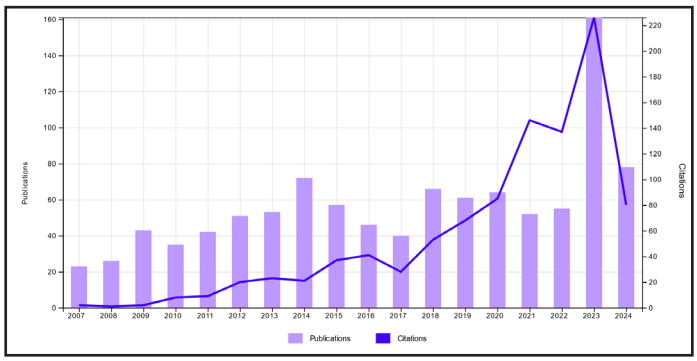

Fig. 1. Graph created from data dated 25/06/2024 [5]

Through this editorial, we would like to share other good recent news and the journal metrics recently published by Clarivate Analytics with you, our valuable followers [6].

According to Journal Citation Reports 2024, *Eur J Ther*'s journal impact factor value is 0.3 (Fig. 2) [6]. We believe that your valuable studies and contributions will increase this value.

Journal Impact Factor ™ is calculated using the following metrics:

$$\frac{\text{Citations in 2023 to items published in 2021 (23) + 2022 (6)}}{\text{Number of citable items in 2021 (48) + 2022 (50)}} = \frac{29}{98} = 0.3$$

Fig. 2. 2023 journal impact factor of the Eur J Ther according to Journal Citation Reports for 2024 [6].

The most pleasing result in the Journal Citation Reports 2024 data [6] is that the Journal Impact Factor Quartile value of *Eur J Ther*, which is in the *Medicine, General & Internal Category*, was determined as Q3. The Journal Impact Factor (JIF) Quartile for the *Eur J Ther* has been calculated for the first time this year, and we are delighted to observe that it is the Q3. In other words, according to the Journal Impact Factor value, *Eur J Ther* ranks 243rd among 325 journals in the *Medicine, General & Internal Category* (JIF Rank 243/325). However, we know we should do our best to go one step further and reach better levels.

As Stephen Hawking says, *"However difficult life may seem, there is always something you can do and succeed at."*

We look forward to sharing more good news with you.

Yours Sincerely,

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European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):e28-e29.
https://doi.org/10.58600/eurjther2201

Special Editorial

Hello AI: Is it Time for A Revolutionary Change in the Health Professional Education System?

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Received: 2023-05-18 **Accepted**: 2024-06-09 **Published Online**: 2024-06-11

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ABSTRACT
The integration of Artificial Intelligence (AI) into healthcare and health professional education has become imperative. This editorial examines how AI technologies, including large language models (LLMs) and extended reality (XR), reshape medical education. We discuss the transition from traditional teaching methods to AI tools, emphasising the need to incorporate AI and programming skills into the medical curricula. Recent advancements such as ChatGPT and BioMedLM have demonstrated the potential of AI to enhance educational methodologies and improve competency assessments. We advocate the adoption of AI in education in order to prepare future healthcare professionals for technologically advanced landscapes.

Keywords: Artificial Intelligence, Medical Education, Competency-Based Education, Extended reality, Virtual Reality, Curriculum development

We did not expect Artificial Intelligence (AI) to move inside health care and health profession education. Recently, there has been a significant rise in papers on AI in healthcare and health professions education, starting from the role of Large Language Models (LLM) in medical sciences to how ChatGPT is cracking most of the examinations in the world [1-3]. We can also say that research papers on AI and Medical sciences are giving tough fights to the number of papers on COVID 19. Various LLMs exist for biomedical sciences, and new daily models are being built from scratch. Stanford is one of the pioneers of BiomedLM, whose dataset has already cleared the USMLE exam [4].

During my undergraduate years, we were in the education system where we had printed exam papers, books from the library, and overhead projector for presentations in which we had to buy the transparent plastic and write over it and present it. This was a different period. While being in the education system for almost 15 years, we have seen a paradigm shift to the Internet, PowerPoint presentations, teaching, and exams on computers using different learning resource management and real-time exam software. Students now hardly use pens, and they mostly use tablets and computers in the education system. Educational assessment and evaluation, teaching, and learning are all computer based.

Just some days ago, open AI launched ChatGPT 4o, i was awestruck with its capabilities, which can be a game changer

even for health sciences. I did not expected to grow this much from ChatGPT 3.5 to 4 and now ChatGPT 4o. Various generative AI are coming up daily, including Med-Gemini which is giving a promising home to revolutionise the health professions education and health sciences. It is a pure pandemic of AI which is growing not only daily, but also every second. The students used GenAi for their studies, assignments, exams, and mock practices.

The question I have for the us is, with this rise -

Will students now need PowerPoints?

Will they read books?

They have everything on their fingertips and millions of bytes of data on their hands. Yesterday, some of my students came with Virtual reality (VR) headsets and showed me a simulated OSCE app which was an exception, with a simulated patient examination. With the rise of AI and the metaverse, we are witnessing a paradigm shift in the education system. The question now arises to use the existing education system of teaching and assessment with the challenges we face with the rise of AI. Yes, we have an AI plagiarism detector, but there is software to neutralise it. My concern is that we should consider upgrading the teaching and assessment methods that we use. We need to inculcate AI not only in practice but also in the curriculum [5]. Therefore, we need to consider the grading system. I feel that we need to think about measuring competency more than just a quantitative analysis of marks. Do we really need conventional rubrics for grading systems, do we need to improvise it with recent evolution or AI, or do we need to start using upgrading and test the competencies? I will keep this question open for us to think and act.

I strongly advocate having a course on AI and teaching Python at the undergraduate level. The next generation of doctors will surely need it, and it is the need of time. We cannot deny that we will see a greater increase in AI, ML, and robotics in the future. From ultramodern AI based hi-tech hospitals to telemedicine using virtual reality is the reality right in front of our eyes [6]. We are the part of change, and I really feel that academicians and practitioners in health sciences should not only be users but also important contributors to the emerging time of AI and technology. It is a peak time for us to get involved.

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European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):249-257.
https://doi.org/10.58600/eurjther2018

Original Research

Segmentation of Pneumothorax on Chest CTs Using Deep Learning Based on Unet-Resnet-50 Convolutional Neural Network Structure

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Received: 2024-01-22 / **Accepted:** 2024-02-25 / **Published Online:** 2024-02-25

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ABSTRACT

Objective: Pneumothorax refers to an abnormal accumulation of air in the pleural cavity. This condition is significant in terms of health and can provide a life-threatening risk, particularly when it is extensive or occurs alongside other medical conditions. Nevertheless, the scarcity of work on chest CT segmentation arises from the challenge of acquiring pixel-level annotations for chest X-rays. This paper presents and assesses a deep learning approach utilizing the Unet-Resnet-50 convolutional neural network architecture for accurately segmenting pneumothoraces on chest computed tomography (CT) images.

Methods: We employed a private dataset including 2627 manually annotated slices obtained from 16 patients. We assessed the model's performance by measuring the dice similarity coefficient (DSC or F1 score), accuracy, area under the curve (AUC), precision, and recall on both the validation and test sets.

Results: The binary accuracy of the test set was 0.9990; the precision was 0.9681; and the DSC was 0.9644. Although it contains less data (16 patients), we found that our deep learning-based artificial intelligence model has effective and compatible results with the literature.

Conclusion: Deep learning models that will be used to detect common pathologies in thoracic surgery practice, such as pneumothorax, to determine their localization and size, will provide faster diagnosis and treatment to patients, and especially improve radiology workflow.

Keywords: Pneumothorax segmentation, Deep learning, Convolutional neural networks, Medical imaging, Artificial intelligence

INTRODUCTION

A pneumothorax, characterized by an unusual accumulation of air in the pleural cavity, is a significant medical issue that can be life-threatening when it is extensive or occurs alongside other medical conditions [1].

Chest X-rays are typically used to diagnose patients with pneumothorax, as they can offer a rough estimate of the volume of pneumothorax. Nevertheless, the assessment of volume in a single X-ray image is inaccurate and lacks consistency. Moreover, distinguishing pneumothorax from similar lung conditions as bullae and emphysema using X-rays is challenging. Consequently, chest computed tomography (CT) scans are now frequently employed to resolve the previously described concerns [2].

In the field of medical image processing, convolutional neural networks (CNNs) have demonstrated significant promise as deep learning-based technologies [3]. Fully convolutional networks, along with their subsequent extensions such as U-Net, have demonstrated remarkable efficacy in the segmentation of medical images, even when trained with a limited quantity of labeled data [3,4]. U-Net and U-Net-like models have shown effective in segmenting many anatomical structures such as the lungs, pulmonary nodules, clavicles, brain, heart, and prostate [1–3,5]

Various U-Net-inspired convolutional neural network (CNN) techniques have been suggested for pneumothorax identification using image-level annotation (classification) on chest X-rays [1,3,6–16]. Lesion semantic segmentation in medical imaging is a crucial tool for facilitating lesion analysis and therapy planning. Nevertheless, the scarcity of work on pneumothorax segmentation on chest x-rays is attributed to the challenges associated with acquiring pixel-level annotations for this condition [1].

The speed of pneumothorax segmentation on a chest x-ray is relatively high, but its accuracy may be worse when compared to segmentation on a CT scan [17]. Performing manual volume assessment on CT scans is a time-consuming task that is possible to carry out in clinical practice [18]. While there are several publications that utilize deep learning algorithms to segment the pneumothorax area on chest x-rays [1,5,19,20], the number of papers that focus on chest CT and employ deep learning, particularly convolutional neural networks, for pneumothorax segmentation is significantly lower [2,21].

The objective of this project was to create a deep learning method using a convolutional neural network to accurately perform semantic segmentation on chest CT scans. Maybe this will provide pneumothorax patients with a faster diagnosis and an earlier treatment chance.

Main Points:

- Pneumothorax, an abnormal air accumulation in the pleural cavity, is a significant health problem and can be life-threatening.
- Deep learning, particularly convolutional neural networks (CNNs) like U-Net, shows promise in medical image analysis.
- This research successfully proposes a UNet CNN based on ResNet-50 for pneumothorax segmentation on chest CTs.

MATERIALS AND METHODS

The local committee has granted approval for the retrospective analysis of the imaging data for the study (Code: 2011-KAEK-2 No: 2023/2).

Dataset

Routine chest CTs of patients diagnosed with pneumothorax in the thoracic surgery department of the university hospital between 2021 and 2022 were obtained from the hospital's PACS (Picture Archiving Communication Systems). Following the anonymization process of DICOM (Digital Imaging and Communications in Medicine) files, a random selection of chest CTs from 16 patients was made from the acquired CTs. Two skilled thoracic surgeons utilized the 3D-Slicer, an open-source software, to carefully identify and delineate pneumothorax regions at the pixel level for each axial slice, creating ground truth annotations.

A total of 3737 slices were obtained from 16 individuals, resulting in an average of 164 slices having pneumothorax per patient. The distribution of CT slices is shown in Figure 1. The dimensions of all slices were 512x512 pixels, and the thickness of each slice was 2.5 millimeters.

Pre-processing

The DICOM images in the dataset undergo preprocessing through normalization, which involves adjusting the Hounsfield unit (HU) values to a range of 0 to 1. This is done to enhance the performance of the model and avoid the influence of excessively high values.

Creation of Training and Test Sets

The dataset was randomly divided into three sets using the train_test_split method from the Sklearn package. The training set consisted of 2391 slices, which accounted for 64% of the dataset. The validation set contained 598 slices, representing 16% of the dataset. The remaining 20% of the dataset was allocated to the test set, which consisted of 748 slices. The training set was used for model training. Hyper-parameter optimization was conducted on the validation set. The test set was only employed once, solely for the ultimate assessment of the current model's

precision. The table provided, Table 1, displays the data and pixel distribution throughout the training, validation, and test sets.

Model Architecture

The model architecture was constructed utilizing a Python library that is open-source and relies on Keras and TensorFlow. This library, known as segmentation models, specializes in picture segmentation using neural networks [22]. A convolutional neural network (CNN) model was constructed using the UNET architecture and the Resnet-50 encoder backbone. Figure 2 displays the structure of a Resnet-50 neural network model. The model comprises a grand total of 32,554,836 parameters, out of which 32,507,282 are eligible for training. The Adam optimizer was utilized with a learning rate of 1e-4. For model training, a hybrid of Binary Cross-Entropy (BCE) and Jaccard loss was employed. The training process was terminated prematurely using the validation set loss after 8 epochs, when patience was set to that value. The model training process was initiated with 1000 epochs and a batch size of 64.

Experimental Setup

Training was carried out on Google-Colaboratory® using Python 3.8.16 and Keras 2.9.0 with Tensorflow 2.9.2 as a backend on Google Compute Engine with Graphical Processing Unit (GPU).

Evaluation Metrics

In order to assess the model's performance, we employed various metrics including the dice similarity coefficient (DSC or F1 score), accuracy, area under the curve (AUC), precision, and recall. These metrics were applied to both the validation and test sets. The outcomes of each pixel were tracked, distinguishing between true positives, false positives, true negatives, and false negatives. The dice similarity coefficient (DSC) is the primary parameter used to validate and analyze the performance of medical image segmentation [23].

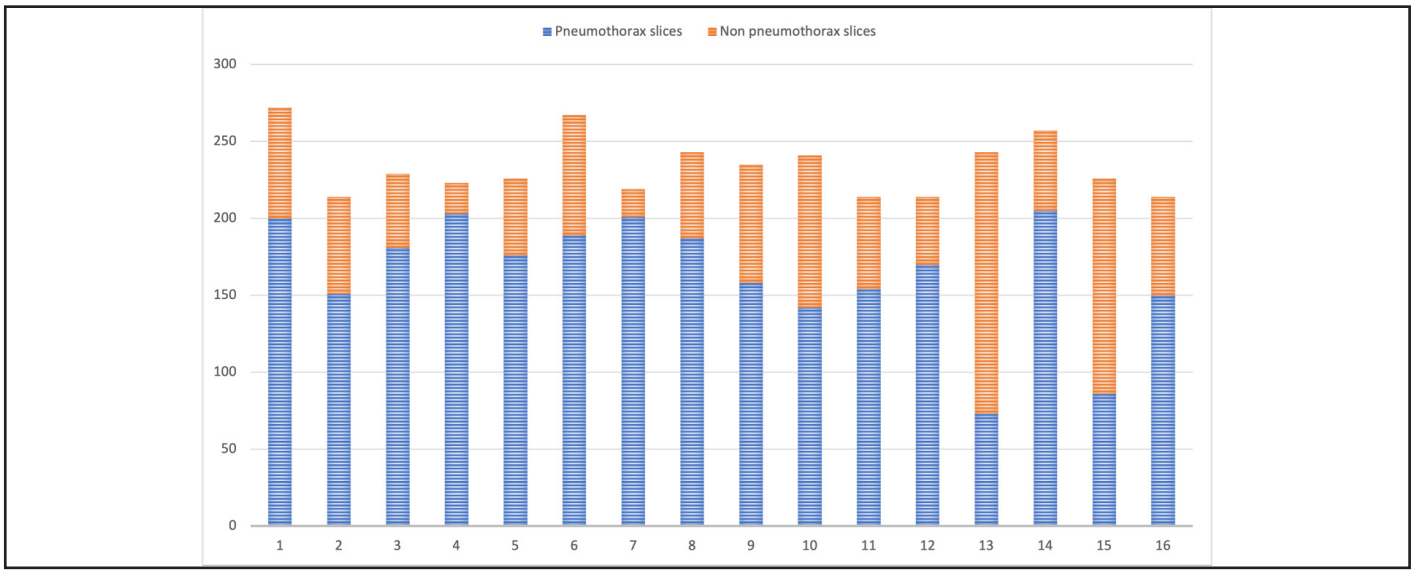

Figure 1. Distrubution of CT slices

Table 1. Data and pixel distrubution of dataset

	Training set	Validation set	Test set	Predicted	Total
Total slices	2391	598	748	748	3737
Non-pneumothorax slices	717	164	229	239	1110
Pneumothorax slices	1674	434	519	509	2627
Average pneumothorax pixels per slice	5244.37	5341.12	5405.43	5527.56	5292.17
Total pneumothorax pixels	8779077	2318050	2805419	2813530	13902546
Total pixels	626786304	156762112	196083712	2813530	979632128

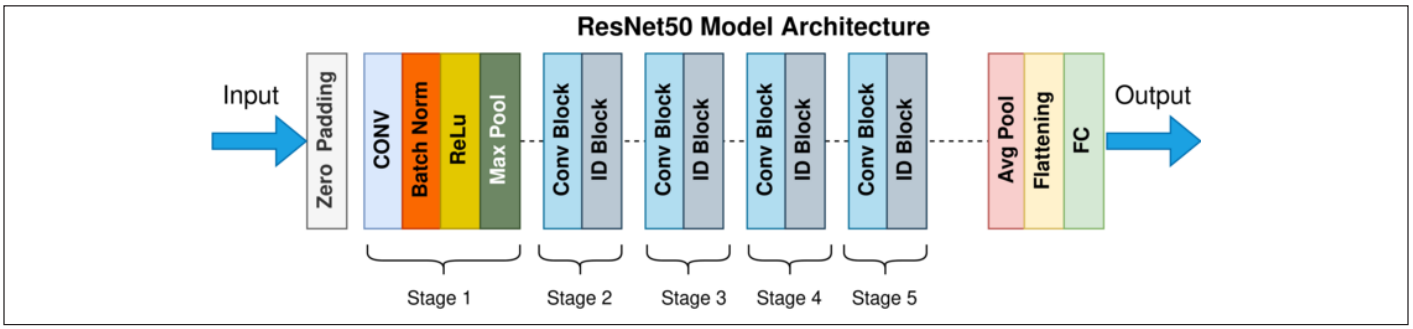

Figure 2. Sample ResNet neural network model structure

RESULTS

The training was completed at the 57th epoch as a result of early stopping. A total of 25.3 GB CPU Ram and 38.9 GB GPU Ram were used for training. The execution time for the training was approximately 46 minutes and the computations for the test set took 31 seconds on the same Google-Colaboratory® environment.

Following the completion of training and hyper-parameter tweaking, the model's performance was assessed using a multitude of indicators. Table 2 displays the model's segmentation performance on the validation and test sets. Figure 3 displays the incremental improvement in performance with each period of the training process.

The binary accuracy of both the validation and test sets was 0.9990, with a validation loss of 0.0729 and 0.0757, respectively. The area under the receiver operating characteristic curve (AUC) was 0.9962 and the Dice similarity coefficient (DSC) was 0.9657 in the validation set. In our training and validation set, we assess the true positive, false positive, true negative, and false negative values for each pixel.

The evaluation of the segmentation performance was also conducted on a separate test set. The test set comprises data that the artificial intelligence model has not been exposed to during its training phase. The precision on the testing set was 0.9681, the recall was 0.9648, and the dice coefficient was 0.9644.

Figure 4 shows instances of segmentation outcomes for dicom pictures obtained from random slices. The first image represents the unmodified CT slice, the subsequent image shows the exact mask, and the last image demonstrates the predicted mask. Additionally, an image is included that displays both the accurate annotation of the ground truth and the predicted mask.

Table 2. Segmentation performance of the model

Metric	Training set	Validation test	Test set
Loss	0.0407053	0.0729687	0.0757
AUC	0.996446	0.996279	0.7265
Binary Accuracy	0.999513	0.999054	0.9990
Binary IoU	0.982674	0.982674	0.9669
Mean IoU	0.690134	0.707968	0.6883
Precision	0.982771	0.978086	0.9681
Recall	0.982476	0.984776	0.9648
True Positive	8625236	2242176	4943309
True Negative	617856000	154367216	347559360
False Positive	151207	76839	162979
False Negative	153841	75874	180160
F1 score (DSC)	0.980604	0.965768	0.9644
IoU score (Jaccard index)	0.961969	0.933909	0.9313

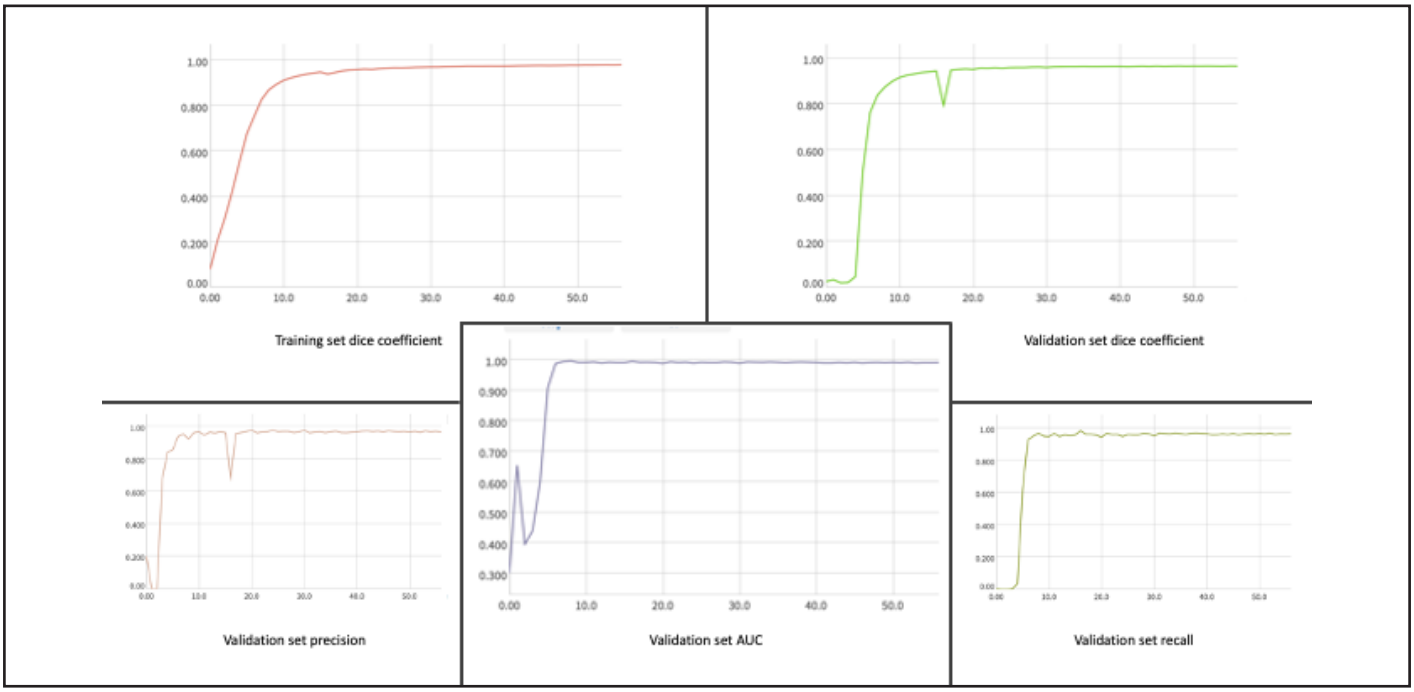

Figure 3. Performans metrics of deep learning model

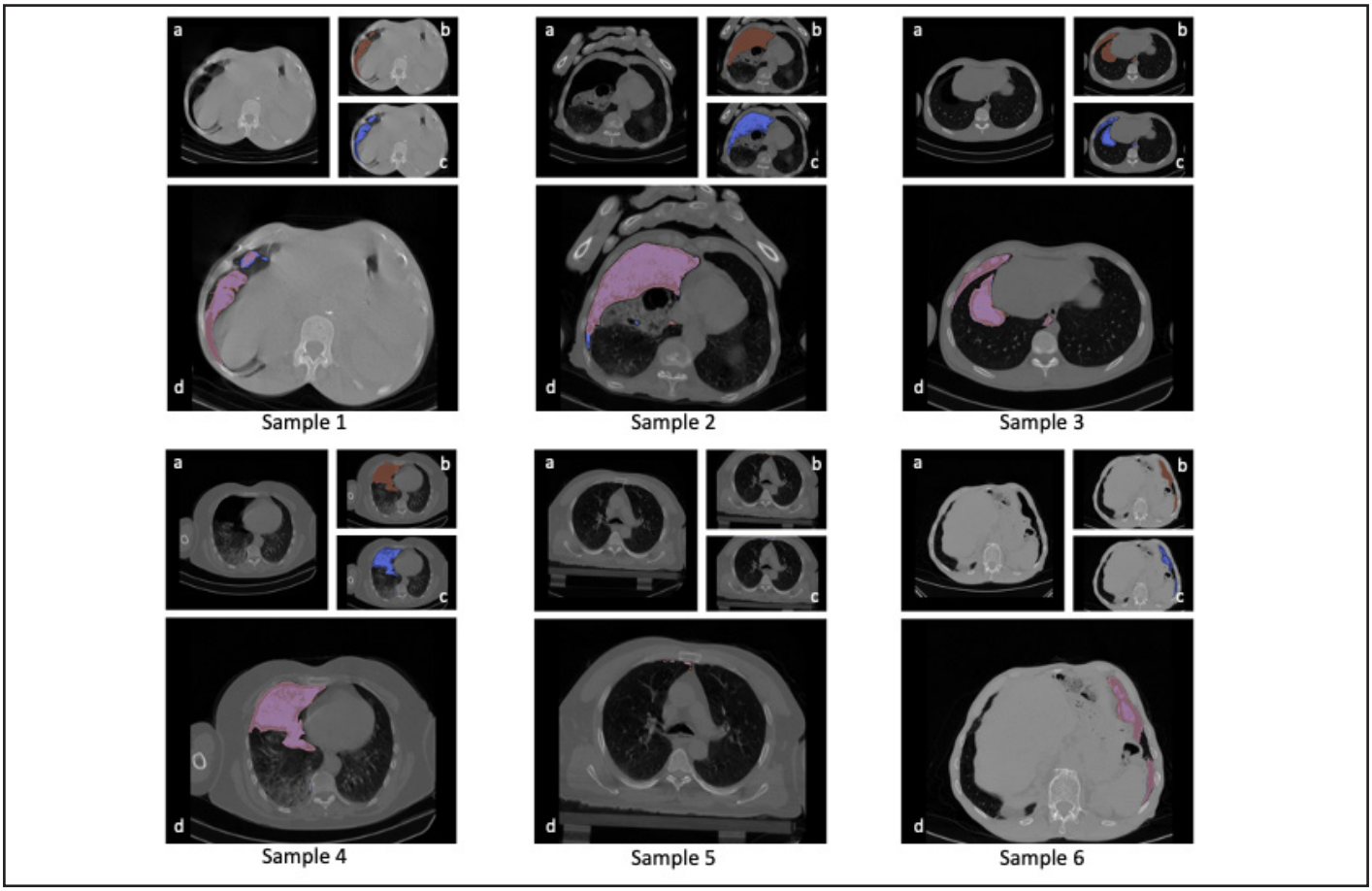

Figure 4. Example CT scans and corresponding segmentations. a. Initial CT image b. Accurate annotations c. Segmentation prediction d. Merged ground truth and predicted segmentations.

DISCUSSION

This paper introduces and assesses a deep learning approach utilizing the Unet-Resnet-50 convolutional neural network architecture to segment pneumothorax on chest CT scans. We utilized a private dataset including 2627 carefully annotated slices obtained from 16 patients diagnosed with pneumothorax. The dataset contained a total of 3737 slices.

The test set evaluation yielded a binary Intersection over Union (IoU) of 0.9669 and a dice score of 0.9644 for this model. Röchrich et al. [21] present their segmentation model based on UNet architecture, achieving an average precision of 0.97 and a dice similarity coefficient of 0.94. The model was evaluated using a private dataset consisting of 2487 annotated slices from 43 patients. They marked one slice out of every five to ten slices and automatically filled in the missing slices in between. In contrast, we carefully annotate each every slice in a manual manner to create accurate ground-truth annotations. The improvement in our dice coefficient may be attributed to this factor.

The study conducted by Wu et al. [2] focuses on the segmentation of pneumothorax on CT sections. In this study, they performed a comparison of 9 distinct convolutional neural networks that resemble UNet architecture. Their confidential dataset comprises 12,535 CT slices obtained from 60 patients diagnosed with pneumothorax. The researchers examine various neural networks, such as Unet, Resnet-Unet, MultiRes-Unet, MFP-Unet, Dilated-Unet, Attention-Unet, and PSP-Net. The Unet++ model yielded the highest dice coefficient scores, achieving 0.9938 for a big pneumothorax and 0.9592 on average. The results of our investigation indicate that the validation set achieved a dice coefficient score of 0.9657, while the test set had a slightly lower value of 0.9644. According to our perspective, the primary determinant influencing the model's performance is the precision with which the ground truth annotation is conducted. For ground truth annotation, each individual pixel must be determined independently. Identifying whether each pixel falls inside the pneumothorax region is challenging, particularly in CT scans that contain artifacts and at the corners.

Ibtehaz et al. [4] sought to enhance spatial resolution by incorporating a third dimension into 2D images. They established a 3D Unet model called MultiResUnet and evaluated its performance on five distinct heterogeneous datasets, including magnetic resonance images from the BraTS17 database. Wu et al. [2] conducted a study on pneumothorax CT scans using the MultiResUnet model. They discovered that MultiResUnet achieved the highest level of accuracy in segmenting big pneumothorax. However, the improvement in the average dice coefficient was only small, with values of 0.9866 and 0.9592, respectively. Reiterating, we achieved nearly identical outcomes in the model we employed, with a dice coefficient of 0.9644 in the test set.

Deep learning models developed on medical images with artificial intelligence are basically divided into two groups. In classification problems, it is tried to determine whether the relevant pathology is present in the medical image given. In segmentation problems, besides the presence of pathology, the location of the pathology is tried to be determined. In order to perform the segmentation, the artificial intelligence model makes a separate prediction for each pixel in the image.

There are many studies in the literature about x-ray classification of pneumothorax [6–16]. Deep learning studies using DICOM CT images for pneumothorax segmentation are very rare due to the intense processing power required. Each thorax CT series contains approximately 200 tomography sections with 512*512 resolution (for 2.5 mm thickness). This means that approximately 52,428,800 pixels are calculated separately for a patient. Some studies on segmentation of other organs and pathologies are available in the literature [3]. However, apart from the studies mentioned in detail above [2,4,21], we could not find any research in the literature that tried to develop a CNN model that could segment pneumothorax using CT slices. It is likely that as the chance of researchers to access high processing power increases, artificial intelligence studies using medical images such as CT, MR and PET, which require many processing, will increase.

Several research have conducted pneumothorax segmentation on x-ray images [1,1,5,20]. Wang et al. [5] created a convolutional neural network named CheXLocNet, which is built upon Mask R-CNN. They applied this model to analyze 12047 X-ray pictures from the "SIIM-ACR Pneumothorax Segmentation Competition" database on Kaggle®. The metrics assessed include AUC, F1 score, sensitivity, specificity, and positive predictive value (0.86, 0.64, 0.82, 0.92, and 0.65, respectively).

In their publication, Wang et al. [1] present an article on ScSE-Dense Net, a convolutional network that is fully implemented. The model was tested using a 11051 chest x-ray, which consisted

of a 5566 case of pneumothorax and a 5485 case of non-pneumothorax. The segmentation analysis yielded a pixel-wise accuracy of 0.93 and a dice similarity coefficient (DSC) of 0.92. The obtained results exhibit higher performance with values of 0.9990 and 0.9644, respectively.

Feng et al. [19] performed a CNN-based artificial intelligence model on the CANDID-PTX dataset, which contains 19237 chest x-rays of the New Zealand population. DeepLabV3+ and Effientnet-B3, the models with the best segmentation performance they found, have lower dice coefficient than ours (0.91, 0.9644, respectively).

Limitations

In the field of artificial intelligence, the effectiveness of models is directly related to the magnitude of the dataset. Despite utilizing a dataset with a smaller amount of data compared to other studies [16], our achievement rates were on the same level as those of analogous studies documented in the literature. The reason why this gap is bridged is due to the presence of similar patterns in medical imaging.

CONCLUSIONS

This paper introduces a UNet convolutional neural network that utilizes a ResNet-50 backbone for the purpose of segmenting pneumothorax on chest CT scans. Experiments on our chest CT dataset show that our deep learning-based artificial intelligence model has results effective and compatible with the literature. Studies on the segmentation of medical images allow to better distinguish pathological events from normal anatomical tissues and focus on this area. In addition, deep learning models that will be used to detect common pathologies in thoracic surgery practice, such as pneumothorax, to determine their localization and size, will provide faster diagnosis and treatment to patients, and especially improve radiology workflow. Further studies on the subject are needed to develop better models especially on 3D images likes CT and MRI.

Funding: No funding was received for this work.

Data availability statement: Model structure and python codes are available publicly at Github Repository (***). Due to its sensitive nature the dataset (DICOM images and pixel data) analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Authorship confirmation/contribution statement: G.A.: Conceptualization, Methodology, Software, Data Curation, Writing - Original Draft. T.Y.I.: Investigation, Resources, Data Curation, Writing - Review & Editing.

Conflict of Interest: We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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How to Cite;

Gencer A, Toker YI (2024) Segmentation of Pneumothorax on Chest CTs Using Deep Learning Based on Unet-Resnet-50 Convolutional Neural Network Structure. Eur J Ther. 30(3):249-257. https://doi.org/10.58600/eurjther2018

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):258-266.
https://doi.org/10.58600/eurjther2002

Original Research

Evaluation of Automated Mammographic Density Classification in Tomosynthesis: Comparison with Radiologists

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Received: 2024-01-10 **Accepted:** 2024-03-27 **Published Online:** 2024-03-29

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ABSTRACT

Objective: Breast cancer screening is a valuable field of health research conducted through mammography. However, mammography evaluation is the examination with the most frequent lack of to agrement among radiologists. In this study we aimed to show the compatibility of mammographic density classification with a new software, Bellus Breast Density Measurement Software (Option), with visual examination.

Methods: The mammographic density classification of 500 patients was retrospectively determined by five radiologists with varying levels of experience, according to the 5th version of the breast imaging reporting and data system (BIRADS). The mean age of 500 women included in the study was calculated as 53.8±10.08. The obtained data were compared with the Bellus software mammographic density classification of the same patients. Then, the visual evaluation and the compatibility of the Bellus software and the readers were compared.

Results: The agreement between the Bellus software and all five readers was poor (kappa value 0.07-0.12). The agreement of the readers with each other is moderate-good (kappa value 0.054-0.64). The Intraclass Correlation Coefficient (ICC) value for the five separate readers was calculated to be 0.80, indicating good compatibility, while the ICC value for the Bellus software with the five separate readers was calculated to be 0.74, indicating moderate compatibility. The Friedman test revealed that while the mammographic density classification of each reader remained consistent, the classification provided by the Bellus software differed.

Conclusion: Bellus Breast Density Measurement Software (Option) diagnostic accuracy is lower than visual examination. We recommend that the manufacturer develop the software.

Keyworlds Bellus software, mammographic density, automatic.

INTRODUCTION

Breast cancer is observed in high incidence and mortality for women in the world. According to the latest updated report of the American Cancer Society; breast cancer constitutes 30% of cancers in women and it is predicted that there will be 297,790 new cases in 2023. In addition, the incidence rate of breast cancer increases 0.5% each year [1]. For this reason, breast cancer screening programs play a vital role. Significant advances have recently occurred in the diagnosis and treatment of breast cancer, which has reduced mortality rates. Breast cancer screening is performed by mammography according to the breast imaging reporting and data system (BIRADS) all over the world. In our

country, breast cancer screening is performed once a year for women over the age of 40. For patients in the high-risk group, screening is performed at an earlier age. These; family history, BRCA gene mutations, patients receiving radiotherapy to the chest area, and patients with high-risk pathology results such as atypia in previous breast biopsies [2]. In the presence of dense breasts in mammography, additional imaging is needed, and in this case, it is often evaluated with supplemental scanning ultrasonography [3,4].

Volumetric mammographic density (MD) defines the ratio of the percentage of dense tissue to the whole breast. On the image, it is related to the attenuation value of X-rays in the breast tissue [5]. Fat tissue appears radiolucent on mammography, which is dark on mammography. Fibroglandular tissue consists of fibroblasts, epithelial cells, and connective tissue cells, radiologically dense and brightly visible on mammography. According to BIRADS, breast density is divided into 4 major categories. These categories are defined as follows: Category A represents completely fatty tissue (5-24% fibroglandular tissue), B represents diffusely located fibroglandular tissue (25-49% fibroglandular tissue), C represents heterogeneous density (50-75% fibroglandular tissue), and D corresponds to dense breast density (75% and more fibroglandular tissue). In BIRADS version 5, categorization was made only by visual evaluation without including percentages in density categorization [6]. This classification is made visually by radiologists all over the world. Several software programs have been developed to automatically perform this subjective classification and quantify breast density. [7,8]. Dense breast definition defines categories C and D. Dense breast has two major clinical conditions. The first is that it reduces the sensitivity of mammographic screening and the second is that it is an independent risk factor for breast cancer [9,10]. As a result, dense breast tissue and cancerous tissue share similar attenuation characteristics, causing both to appear bright on mammography. Dense tissue and cancer tissue have similar attenuation and both appear bright on mammography.

Tomosynthesis or 3D mammography was approved by the US Food and Drug Administration (FDA) in 2011 for use in all clinical indications used for mammography. In this technique, the X-ray tube moves at a certain angle arc in the compressed breast tissue to obtain an image. In this way, images with smaller doses are obtained at multiple angles [11]. It has been shown that this method, especially in dense breasts, is more sensitive in detecting cancer compared to mammography [12,13].

Mammographic density classification is visually subjective, and differences in intraobserver and interobserver classification have been shown in the literature [14]. In addition, although it is not the standard method recommended for MD until now, visual assessment is performed with semi-automatic method and automatic methods. Studies in the literature compare these methods both with visual evaluations by radiologists and among themselves. [15,16]. These programs are; Cumulus (Sunnybrook Health Sciences Centre, Toronto, ON, Canada), Quantra version 2.0 (Hologic Inc, Bedford, MA, USA), Volpara Density Algorithm 1.5.0 (Volpara Health Technologies, Wellington, New Zealand), Densitas version 2.0.0 (Densitas Inc, Halifax, NS, Canada). However, there is currently no literature on the use of the Bellus automatic breast density measurement system specifically designed for tomosynthesis mammography devices developed by Fujifilm (Tokyo, Japan).

The aim of our study is to assess the agreement among observers in breast density classification using tomosynthesis, and to investigate the agreement among observers using the Bellus automatic breast density measurement system with the participation of different observers.

Main Points:

- There is interobserver variability in determining mammographic density rates.
- Bellus software, which is automatic breast density calculation software, makes more errors than expected.
- In the Middle Black Sea Region, there are more cases in the nondense (A and B) mammographic density group.

MATERIALS AND METHODS

The study was conducted retrospectively following approval from the local ethics committee (approval number: 22-KAEK-286, dated 22.12.2022). Our study adhered to the principles outlined in the Helsinki Declaration.

Case Selection

The mammography images of 650 randomly selected cases, who came to breast screening in accordance with national standards, were analyzed retrospectively. Patient selection was made randomly and is thought to objectively reflect the society. Cases

who received hormone therapy before, cases with a history of breast cancer, cases who underwent breast surgery, cases with suspected malignancy in the breast during the examination, and cases with a difference in density between the two breasts were not included in the study. In addition, patients who could not perform adequate breast compression, had intense artifacts in the images, and patients in whom most of the breast was not included in the image area were not included in the study (Table 1). Ultimately, 500 patients were included in the study. The mean age of 500 women included in the study was calculated as 53.8±10.08.

Table 1. Mammographic Density classification rates of each reader and Bellus software.

Readers	A	B	C	D	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
First	60 (12)	269 (53.8)	152 (30.4)	19 (3.8)	500 (100)
Second	68 (13.6)	196 (39.2)	182 (36.4)	54 (10.8)	500 (100)
Third	60 (12)	244 (48.8)	175 (35)	21 (4.2)	500 (100)
Fourth	64 (12.8)	224 (44.8)	175 (35)	37 (7.4)	500 (100)
Fifth	61 (12.2)	251 (50.2)	136 (27.2)	52 (10.4)	500 (100)
Bellus	210 (42)	245 (49)	42 (8.4)	3 (0.6)	500 (100)

n: number

Tomosynthesis Technique and Protocol

Images were obtained with the Fujifilm AMULET Innovality Digital Tomosynthesis device. The patients were given the maximum possible compression, mediolateral (MLO) and craniocaudal (CC). Due to automatic exposure control (AEC), milliampere-seconds (mAs) and kilovoltage peak (kVp) values differ from patient to patient. These values are in the range of 25-35 kVp and 25-100 mAs. Exposure time is less than 2 seconds and fully automatic exposure technique is used. Sections for tomosynthesis were created on the MLO. MLO images were obtained in such a way that the lower end of the pectoral muscle ends at the inferior level of the imaginary line passing through the areola and the inframammer fold is visible. CC images were obtained with the pectoral muscle visible in the posterior. No contrast agent was used.

Image Evaluation and Bellus Breast Density Measurement

The images were evaluated independently by 5 radiologists with different breast radiology experiences (Respectively, their experience was 2 years, 4 years, 9 years, 11 years, 16 years). One of the observers is a junior assistant and the other is a senior assistant. Three observers are radiologists. One of them is a breast radiologist and the other two are nonspecific radiologists. Observers have undergone international breast radiology training. Images were evaluated from a 21.3 inch 3MP IPS Screen medical monitor via Fujifilm Mammography Workstation (3000AWS7.0 Option) and Sectra IDS 7 PACS (Picture Archiving and Communication Systems). Readers performed the assessment according to BIRADS version 5. Breast densities of the patients were recorded as A, B, C, D (Figure 1). Observers made the BIRADS category in a non-quantitative way based on their own experience.

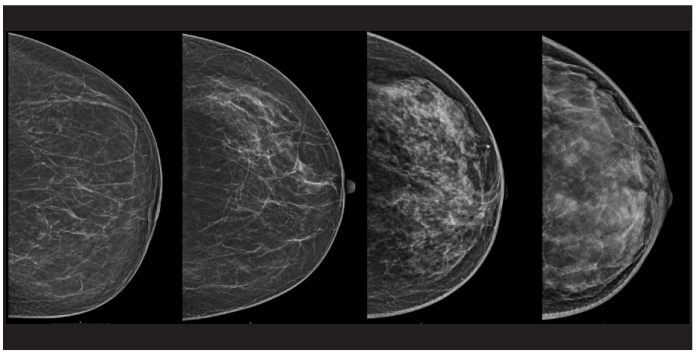

Figure 1. A-D mammographic density on CC radiographs of the left breast (left to right respectively).

Bellus Breast Density Measurement Software (Option) automatically categorized breast density into 4 groups using mammography images and exposure data. The calculation was categorized into 4 groups based on mammarian gland ratio (percentage), fat volume (cm^3) and total volume of the breast (cm^3) data, and threshold values. Bellus software calculates a percentage based on the ratio of fibroglandular tissue to fat tissue present in the image. This calculation is performed according to the density difference between fibroglandular tissue and fat tissue. The software performed these calculations on tomosynthesis data. These measurements were made by the software on 3D breast maps (Figure 2). In this categorization, the threshold values over the percentage of mammarian glands are; determined as 0-15% for group A, 15-35% for group B, 35-60% for group C and 60-100% for group D. These ranges are determined by the Bellus software.

Bellus Breast Density Measurement Software (Option) is a software belonging to Fujifilm, a Japanese company.

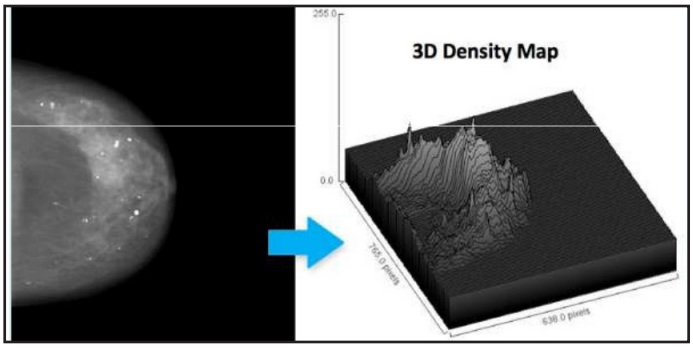

Figure 2. Schematic representation of the volumetric calculation of breast gland ratio (as a percentage), fat volume (cm^3) and breast volume (cm^3) by the Bellus Breast Density Measurement Software (Option) software developed by Fujifilm (Courtesy of Volpora Health).

Statistical Analysis

The SPSS 24 statistical software package (IBM Corp., Armonk, NY, USA) was used for all data analysis. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean, deviation, and minimum-maximum. It was checked with Friedman test whether 5 different readers and Bellus Breast Density Measurement Software (Option) median, Percentile 25 and 75 ratios were the same. Correlation between Cohen Kappa test and readers and Bellus Breast Density Measurement Software (Option) was examined. Kappa coefficient; if it is less than 0, weak agreement, 0-0.20 as insignificant agreement, 0.21-0.4 as low agreement, 0.41-0.6 as medium agreement, 0.61-0.8 as high agreement, and 0.81-1 as excellent agreement. The Intraclass Correlation Coefficient (ICC) value of 5 different readers and the Intraclass Correlation Coefficient value of the software with 5 different readers were calculated. Having this value below 0.5 is poor; moderate between 0.5-0.75; 0.75-0.9 good and above 0.9 were accepted as excellent agreement [17]. One-way analysis of variance (ANOVA) was used to compare the mean ages of each mammographic density group for each reader and software. Tukey HSD test was used for multiple comparison. P value <0.05 was considered statistically significant.

In a 6x4 design with 6 readers evaluating in 4 groups, approximately 500 samples will be studied with 80% power, 5% type I error and an effect size of 0.10. Sample size was calculated with the G*Power program (version 3.1.9.4).

RESULTS

All five readers included patients in the B, C, A and D categories, respectively, in mammographic density (From the highest number of patients in the groups to the lowest number). However, Bellus software included patients in the B, A, C and D categories, respectively, in mammographic density. (Table 2).

The dense breast category (groups C and D) was detected by the readers and the software at the following rates: first reader 171 (34.2%) patients, second reader 236 (47.2%) patients, third reader 196 (39.2%) patients, the fourth reader identified 212 (42.4%) patients, the fifth reader identified 188 (37.6%) patients, and the Bellus software identified 45 (9%) patients. The rate of nondense breasts was higher for all five readers and Bellus software in the patients included in the study. Dense breast percentage was determined most in the second reader and least in Bellus software.

In the Friedman test, it was determined that the median, Percentile 25 and 75 ratios were the same for five different readers. For Bellus software, the median value is the same, but the Percentile 25 and 75 values are different (Table 3).

In the visual evaluation, the agreement of the readers with each other was calculated as medium and high. In the agreement of the readers with each other, the highest agreement kappa value of 0.66 is between the second and fourth readers, and the lowest agreement kappa value of 0.54 is between the first and second readers. The agreement of each reader with the Bellus software was insignificant. With Bellus software, the highest agreement kappa coefficient was found between 0.12 and the first reader, and the lowest agreement was between 0.04 and the second reader (Tables 4 and 5).

Visually, the Intraclass Correlation Coefficient (ICC) value was calculated as 0.8 (good correlation) for 5 readers and 0.74 (moderate correlation) when Bellus software was included with 5 readers (Tables 4 and 5).

The mean age of 500 women included in the study was calculated as 53.8±10.08. Except for the second reader, no statistically significant difference was found for the C and D groups in terms of mean age in the other four readers ($p<0.001$). However, no statistical significance was found for any group in the mean age of the second reader. In Bellus software, no statistically significant difference was found for both groups C and D, and

groups B and D ($p<0.001$). In each reader and Bellus software, the highest mean age was determined in group A, and the mean age was found in groups B, C, and D with decreasing mean ages, respectively (Table 6).

The results of the power analysis were determined as 80% power, 5% type I error and an effect size of 0.10.

Table 2. Median, percentile 25 and 75 values of each reader and Bellus software in Friedman test.

Readers	Median	Percentile 25	Percentile 75
First	2	2	3
Second	2	2	3
Third	2	2	3
Fourth	2	2	3
Fifth	2	2	3
Bellus	2	1	2

Table 3. Inter-reader agreement

Inter-reader agreement	Kappa value	Agreement Level	ICC value(95%)
First and Second	0.54	medium agreement	0.80 (good)
First and Third	0.63	high agreement	
First and Fourth	0.59	medium agreement	
First and Fifth	0.59	medium agreement	
Second and Third	0.64	high agreement	
Second and Fourth	0.66	high agreement	
Second and Fifth	0.63	high agreement	
Third and Fourth	0.62	high agreement	
Third and Fifth	0.60	medium agreement	
Fourth and Fifth	0.64	high agreement	

Abbreviations: ICC: Intraclass Correlation Coefficient

Table 4. Agreement between readers and Bellus software

Bellus Software	Kappa value	Agreement Level	ICC value (95%)
First	0.12	insignificant agreement	0.74 (moderate)
Second	0.04	insignificant agreement	
Third	0.07	insignificant agreement	
Fourth	0.07	insignificant agreement	
Fifth	0.09	insignificant agreement	

Abbreviations: ICC: Intraclass Correlation Coefficient

Table 5. Average age in Mammographic Density groups of each reader and Bellus software

Readers	Total	Age			
		A	B	C	D
	Average ±SD	Average ±SD	Average ±SD	Average ±SD	Average ±SD
First	53.8±10.08	61.42±9.01	56.21±9.83	47.68±7	44.68±4.28
Second	53.8±10.08	61.46±8.78	56.88±9.64	49.91±8.75	46.13±5.78
Third	53.8±10.08	62.57±8.62	55.96±9.88	48.95±7.83	44.1±2.53
Fourth	53.8±10.08	61.83±8.75	56.57±9.85	48.96±7.85	46.08±6.19
Fifth	53.8±10.08	61.57±9.81	56.15±9.99	48.94±7.09	46.1±5.98
Bellus	53.8±10.08	57.2±9.18	52.51±10.3	45.21±4.67	42.67±4.73

Abbreviations: SD: Standard Deviation

DISCUSSION

We have demonstrated in our study that the new software, Bellus automatic breast density measurement, which assesses through tomosynthesis, exhibits lower accuracy in evaluating breast density compared to visual examination, as determined by multiple readers with varying levels of experience. Additionally, we concluded that there is a good level of agreement among radiologists with different levels of experience who classify breast density through visual examination. Furthermore, we found that the youngest group of breast density patterns is group D, while the oldest group is group A, as identified by both visual radiologists and the Bellus software program.

Our study aims to evaluate a novel software for classifying mammographic density through tomosynthesis, a methodology not previously explored. While similar studies have been conducted on single-section mammography images, ours marks the first attempt using tomosynthesis. Furthermore, the involvement of five radiologists with varying levels of experience and the examination of a large number of samples enhance the significance of our study. By employing these methods, we aimed to objectively evaluate mammographic density, a concept previously challenging to classify accurately.

There are numerous studies in the literature that incorporate volumetric estimates for BIRADS. Brandt et al. conducted a study comparing automatic breast density measurement with clinical measurement, revealing medium agreement between Volpara and Quanta software and clinical breast density classification (kappa values: 0.57 and 0.46, respectively) [18]. Another study comparing visual evaluation with Volpara and Quanta software in the 5th version of BIRADS found low to medium agreement (kappa value: 0.32-0.43) and medium to high agreement (kappa value: 0.54-0.61) [19]. When comparing breast density studies with BIRADS version 4, Volpara software showed low to high agreement (kappa value: 0.4-0.8) and Quanta software showed high agreement (kappa value: 0.63-0.73) [20-23]. In our study, we compared Bellus, a newer software, and found insignificant agreement for each reader (kappa value: 0.04-0.12). Additionally, we observed differences in Percentile 25 and 75 values, although the median value was the same among five observers in the Friedman test. We attribute the lower level of agreement in our study to the novelty of the software we evaluated.

In the literature, mammographic density percentages have been extensively studied for BIRADS version 5. Previous studies have reported varying percentages across different density categories. For instance, one study found that 10% of patients were classified as fatty (group A), 40% as scattered (group B), 40% as heterogeneously dense (group C), and 10% as extremely dense (group D) [24,25]. Another study reported percentages of 3.5%, 22.1%, 54.9%, and 19.5% for groups A, B, C, and D, respectively [19]. Similarly, another study found rates of 1.6%, 14.3%, 69.1%, and 15% in groups A, B, C, and D, respectively [26].

In our study, we observed differences in the rates reported by five observers, excluding the Bellus software, with percentages ranging from 12% to 13.6% for group A, 39.2% to 53.8% for group B, 27.2% to 36.4% for group C, and 3.8% to 10.8% for group D. Initially, we attributed these discrepancies to variations in the studied population. Contrary to previous studies, our study,

conducted in the Central Black Sea Region, found a higher rate of non-dense breasts in our study population. This suggests that mammographic screening may be more sensitive in our society, potentially reducing the need for supplemental screening.

In the literature, the agreement between observers in mammographic density classification has been extensively evaluated, revealing wide variability ranging from poor to perfect agreement (kappa value: 0.02-0.87) [21,26,27]. Some studies reported better interobserver agreement, reaching perfect agreement with kappa values ranging from 0.81 to 0.84.

In our study, we found moderate to high inter-reader agreement (kappa value: 0.54-0.66), with an Intraclass Correlation Coefficient (ICC) value of 0.8 indicating good correlation among readers. We attributed the differences observed in the literature to the varying levels of experience among radiologists. Previous studies have linked inter- and intra-reader variability in mammographic density determination to the differing experiences of radiologists [28].

More objective presentation of mammographic density classification, which is a subjective evaluation, with software will determine the needs of patients for Supplemental Screening more accurately. It will also assist the radiologists in their process of gaining experience.

We believe that the reason the Bellus software provides lower estimates of breast density rates compared to human radiologists is due to its novelty. As the software is still in the testing phase, our initial study highlights the need for improvements. While radiologists typically rely on qualitative assessments in determining breast density rates through their daily practice, software applications like Bellus aim to incorporate more quantitative data into their findings.

Limitations

The limitations of our study include the following: it was a single-center analysis, cases with different mammographic densities of both breasts were not included, and the behavior of the Bellus software in such cases was not tested. Additionally, the rate of dense breasts in our study was low, and we did not evaluate intraobserver agreement. Furthermore, we did not compare the Bellus software program with more common software programs. In the tomosynthesis technique, variations in kVp and mAs values from patient to patient may affect automatic density calculation. Although we do not believe this situation significantly impacts our results, it should be noted as a limitation.

CONCLUSION

A new software program, Bellus Breast Density Measurement Software [Optional function of AMULET Innovality (3000AWS7.0 Option)], has lower diagnostic accuracy than visual examination. We recommend that the manufacturer develop the software. In addition, the relatively higher rate of detection of patients in the nondense mammographic density group in the region we live in (Central Black Sea Region) suggests that there will be a lesser need for Supplemental Screening in this region.

Acknowledgement

We would like to thank Volpora Health for permission to use the schematic image in Figure 2.

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

Funding: No source of funding.

Author Contributions: Conception: HAK; Design: MB; Supervision: EG, Materials: MFB, MEÇ, YB; Data Collection and/or Processing: HAK, MB, EG, YB, MFB, MEÇ; Analysis and/or Interpretation: OD; Literature: HAK, Review: HAK, MB, EG, YB, MFB, MEÇ; Writing: HAK, MB, EG, YB, MFB, MEÇ; Critical; Review: HAK, MB, EG, YB, MFB, MEÇ.

Ethical Approval: This study was approved by the local ethical committee of the city hospital (202/22-KAEK-286) and the procedures were according to the ethical standards of the responsible committee on human experimentation.

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How to Cite;

Kızıloğlu HA Beyhan M, Gökçe E, Birişik Y, Battal MF, Çeker, ME Demir O (2024) Evaluation of Automated Mammographic Density Classification in Tomosynthesis: Comparison with Radiologists. Eur J Ther. 30(3):258-266. https://doi.org/10.58600/eurjther2002

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):267-276.
https://doi.org/10.58600/eurjther2074

Original Research

A Comparison of the Smile Esthetic Understanding of Periodontists, Orthodontists, General Dentists, and Dental Students

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Received: 2024-03-01 **Accepted**: 2024-04-25 **Published Online**: 2024-04-27

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ABSTRACT

Objective: The aim of this study was to evaluate smile esthetics among periodontists, orthodontists, general dentists, and dental students.

Methods: The study consisted of five groups: periodontists, orthodontists, general dentists, fifth-year dental students, and fourth-year dental students. The evaluators used the Smile Esthetics Index (SEI) consisting of 10 items to analyze the natural smile photographs of 15 different individuals. One-way ANOVA was performed for the comparison of group means. The Duncan multiple comparison test was also used to identify different groups. Non-linear principal component analysis was performed to determine the configuration of the relationship between categories of variables in two-dimensional space.

Results: The group with the highest reliability coefficient among the groups was the fourth-year dental students (Cronbach's Alpha = 0.89). This was followed by general dentists, periodontists, fifth-year dental students, and orthodontists. According to the evaluation of the total score averages of the fifteen pictures, a statistically significant difference was observed between the groups (p = 0.041). Accordingly, the fourth-year dental students (5.78 ±1 .13) had a lower total score than the fifth-year dental students (6.56 ± 0.88), and this difference was statistically significant. However, no significant difference was observed between the fourth-year dental students and the general and specialized dentists and between the fifth-year dental students and graduated and specialized dentists in terms of the total score given to the pictures.

Conclusion: It was observed that the reliability coefficient was high in all groups evaluated with SEI. It can be concluded that esthetic perception is formed by actively performing the profession of dentistry, and this situation does not change according to specialization.

Keywords: Esthetics, smiling, tooth

INTRODUCTION

The perception of facial esthetics, where a smile has a positive effect on attractiveness [1,2], is specifically seen as a dominant concern when planning dental treatment [3] because dissatisfaction with one's smile can have a significant impact on self-esteem [4]. This situation is associated with reports that,

when evaluating the general perception of beauty, teeth are considered the second most important facial feature after the eyes [1]. Correspondingly, in modern societies, the esthetic perception associated with smiling can play a prominent role in interpersonal communication. Factors including papillary recession between teeth and gum appearance as well as the midline of the face; the smile line; the size, shape, position, and color of the teeth; and the lip frame are important in the esthetics of a smile. It is crucial to make every effort to plan a harmonious balance that produces the most natural smile in every patient. Therefore, the emphasis placed on soft tissues in the assessment and design of smiles should be the same as that placed on hard tissues because esthetic perception can be achieved with harmony between these tissues. Hence, when a more beautiful smile is obtained through both periodontal and orthodontic interventions, the individual is likely to feel better and more confident.

In recent years the Smile Esthetic Index (SEI), published by Rotundo et al. [5], has been suggested as a reliable method for assessing smile esthetics [5,6]. The index evaluates smile esthetics based on ten variables: smile line, facial midline, tooth alignment, tooth deformity, tooth discoloration, gum discoloration, gum recession, excess gum, scar tissue on the gum, and diastema/lack of papilla. The authors have reported that SEI is a repeatable method and can even be useful in presenting appropriate treatment options for patients [5]. This is because the analysis of a smile by a dentist can contribute to correctly understanding patient expectations and to forming more accurate suggestions during the treatment phase. It can even be used to assess the difference before and after treatment [6].

In the literature, the differences in the main parameters of smile esthetics have been analyzed. The characteristics of esthetic smiles include no deviation or bending in the maxillary midline, a larger number of teeth showing during smiling, the maxillary incisal edges being parallel to the lower lip, and occlusal and commissural planes being parallel to the interpupillary line [7]. Moreover, perception differences, not only with dentists but also among laypeople, have been evaluated [8] Gaikwad et al. [9] conducted assessments among laypeople, dentists, and orthodontists. Smile esthetics have been evaluated both in terms of individuals' own perceptions of their smile quality and using the SEI [10]. However, there is a lack of sufficient studies that evaluate this perception among specialist dentists, general dentists, and dental students who are new to the concept of esthetic perception.

Main Points;

It can be concluded that esthetic perception is formed by actively performing the profession of dentistry, and this situation does not change according to specialization.

Therefore, the aim of this study is to evaluate the SEI by periodontists, orthodontists, general dentists, and dental students and to compare the perception of smile esthetics among these groups. The null hypothesis of our study is formulated as follows: 'there is no difference in the evaluation of smile esthetics among dentists or dentist candidates working in different specialties of dentistry.'

MATERIALS AND METHODS

The study commenced after approval was obtained from the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (Ethics Number 2023/04-08). The sample size was calculated using the G*Power statistical package (version 3.1). It was determined that a total of 125 individuals in five groups were needed, using an effect size of 0.4 and a power of 95 %. The five groups that made up the study were periodontists, orthodontists, general dentists, fifth-year dental students, and fourth-year dental students, with a total of 125 evaluators, each group including 25 evaluators. Each evaluator voluntarily participated in the study and was thoroughly informed about the purpose and methodology of the study; written consent was obtained from each participant. The study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria for the evaluators were as follows:

- The periodontists and orthodontists were required to have a PhD or specialization in the relevant field or to be currently pursuing specialization or PhD training in these branches with sufficient competence and knowledge in the field.
- The general dentists were required to have been actively working for at least two years and not to have specialized or pursued a PhD in any field of dentistry.
- The dental students were required to be in the fourth or fifth year, currently participating regularly in clinical internships, and actively taking on patient treatment.

The inclusion criteria for the individuals in the photographs to be analyzed were limited to individuals older than 20 years, without a history of orthodontic or orthognathic surgical treatment, having healthy and/or reduced periodontium, possessing a complete set of permanent teeth except for the third molars, and having various malocclusions. Subjects were seated with a natural head position on a cephalostat and then photographed from the front; each subject was smiling naturally. The photographs were taken in the same environment and under the same lighting conditions, with the camera (EOS 60D, ISO 200, shutter speed 1/200 sec, F 20, Canon Inc. made in Taiwan) fixed on a tripod, and all photographs were taken in color. Subjects were asked not to wear make-up and to remove piercings, if any, before the photo shoot. The photographs were then transferred to a computer and cropped with vertical (tip of the nose and soft tissue pogonion) and horizontal (a line drawn downwards from the zygomatic prominence) boundaries. All images were later resized to a standard image size. Evaluators analyzed the natural smile photographs of 15 different individuals. The use of the SEI was limited to the presence of teeth, meaning it is applicable only to smiles that show all the teeth and is not referred to in the absence of teeth. The SEI consists of a 10-item review. Each evaluator awarded 1 point for a "yes" response and 0 points for a "no" response to these 10 questions. The 1 or 0 points were attributed according to the presence or absence of the variable in question, respectively. The total score was then calculated by totaling the points attributed to each of the 10 responses.

Statistical Analysis

Descriptive statistics for the continuous variables were presented as mean, standard deviation, and minimum and maximum values while categorical variables were presented as count and percentages. Distribution of data was analyzed with Kolmogorov-Smirnov test. One-way ANOVA was performed for the comparison of group means. The Duncan multiple comparison test was also used to identify different groups. Cronbach's Alpha coefficient was calculated to determine intraclass correlation for the 15 photographs as follows: excellent reliability for $0.90 \leq \alpha \leq 1$, high reliability for $0.70 \leq \alpha < 0.90$, moderate reliability for $0.50 \leq \alpha < 0.70$, and low reliability for $\alpha < 0.50$ [11]**.** In addition, non-linear principal component analysis was performed to determine the configuration of the relationship between categories of variables in a two-dimensional space. Statistical significance level was considered to be five percent, and the SPSS (IBM Corp. Armonk, NY, Ver: 21) statistical program was used for all statistical computations.

RESULTS

The Cronbach's Alpha coefficients for determining the internal reliability for the fifteen smile photographs are provided in Table 1. Accordingly, since the Cronbach's Alpha coefficients for each group are within the range of $0.70 \leq \alpha < 0.90$, high reliability was accepted for all groups. The group with the highest reliability coefficient was the fourth-year students (Cronbach's Alpha = 0.89), followed by general dentists, periodontists, fifth-year students, and orthodontists, in order.

One hundred twenty-five individuals (71 women, 54 men) were included in the study. The distribution of individuals in the groups, their average ages, standard deviations, and minimum and maximum values are shown in Table 2.

The total scores received by each photograph are given in Table 3. Accordingly, the highest score of 10 points was given to photographs 7 and 14 while photograph 12 received zero points from two evaluators.

The average total scores given by the groups for each photograph, the average total scores for the 15 photographs, and the comparative statistics of the groups are shown in Table 4. When evaluating the average score points given to the fifteenth photograph, it was observed that general dentists (6.24 ± 2.47) gave lower scores compared to fifth-year students (5.12 ± 2.02) and orthodontists (4.76 ± 1.80) ($p = 0.044$). According to table, statistically significant differences were found in six photographs (4, 5, 6, 7, 14, and 15) among the groups ($p < 0.05$). The average scores of general dentists (6.56 ± 1.82) for the fourth photograph were lower than those of periodontists (7.76 ± 1.69) and fifth-year students (8.08 ±1 .57); the average scores of orthodontists (6.92 ± 1.49) were lower than those of fifth-year students (8.08 ± 1.57) ($p = 0.015$). For the fifth photograph, fourth-year (9 ± 1.58) and fifth-year students (9 ± 1.70) gave the same average score, and periodontists (7.96 ± 1.30) and orthodontists (7.96 ± 0.88) gave the same average score. The fourth-year students (3.28 ± 1.69) gave a significantly lower average score for the sixth photograph compared to the other four groups ($p = 0.001$). When the score averages for the seventh photograph were examined, the average score of fourth-year students was found to be 7.72 ±2 .03, which was statistically significantly lower than that of fifth-year students and periodontists ($p = 0.011$). While a significant difference was observed among students for the fourteenth photograph ($p = 0.019$), no significant difference was found among graduated dentists regardless of specialization status.

According to the evaluation of the total score averages for the fifteen photographs, a statistically significant difference was observed only between fourth- and fifth-year students (p = 0.041) (Table 4). Accordingly, it was determined that fourth-year students (5.78 ± 1.13) had a lower total score averages than fifth-year students (6.56 ± 0.88), and this difference was statistically significant. However, no significant difference was observed in terms of the total score averages given to the photographs between fourth-year students and general and specialist dentists and between fifth-year students and graduated and specialist dentists.

The two-dimensional configuration of the relationships between the categories of variables is shown in Figure 1. The first dimension explains 45.1 % of the variation observed among the categories of variables while the second dimension explains 25.85 %. Together, both dimensions explain 70.95 % of the variance. On the negative side of the first dimension, scores of 6–8 were observed in fourth- and fifth-year students who were 21–28-year-old males. Evaluating the positive side of the first dimension, it can be said that females who are general dentists, orthodontists, and periodontists in the 29–49 age range tend to give an average score of 3–6. When the positive side of the second dimension, the upper part of the graph, is evaluated, it can be said that males who are general dentists, orthodontists, and periodontists in the 29–49 age range tend to give an average score of 6–8.

Table 1. Cronbach's Alpha intraclass reliability coefficients for fifteen smile photographs

Group	Cronbach's Alpha
Fourth-year dental students	0.89
Fifth-year dental students	0.81
General dentist	0.85
Periodontists	0.83
Orthodontics	0.80

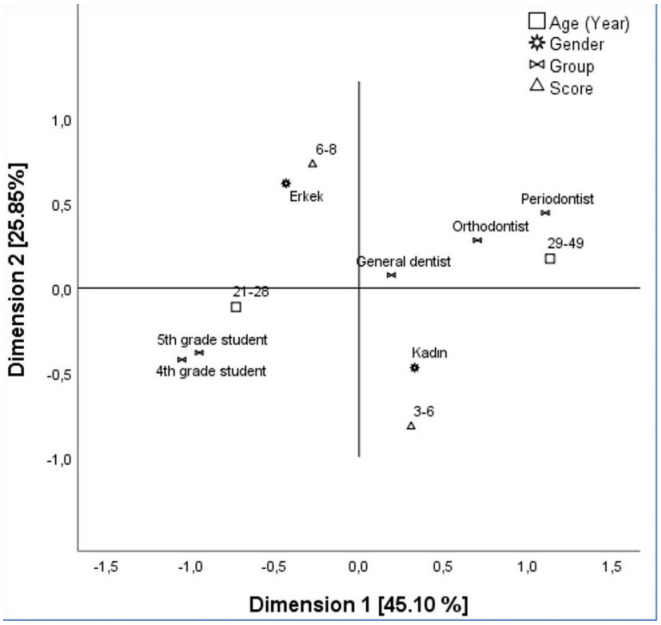

Figure 1. Configuration of the relationships between categories of variables in two-dimensional space

Table 2. The distribution of individuals in the groups, their average ages, standard deviations, and minimum and maximum values

		n	Mean	SD	Min.	Max.
Age	**Female**	71	28.66	6.25	21	49
	Male	54	27.33	6.04	22	43
	Fourth grade students	25	22.16	0.62	21	24
	Fifth grade students	25	23.12	0.60	22	25
	General dentists	25	30.32	5.78	24	42
	Peridontists	25	33.00	5.78	26	49
	Orthodontists	25	31.84	4.69	27	42
	Total	125	28.09	6.17	21	49

Table 3. Statistical evaluation of the total scores of the fifteen smile photographs

		Smile Picture Number														
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Score	**0**	0% (n=0)	0% (n=0)	0.8% (n=1)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	1.6% (n=2)	0% (n=0)	0% (n=0)	0.8% (n=1)
	1	0.8% (n=1)	0% (n=0)	6.4% (n=8)	0% (n=0)	0% (n=0)	5.6% (n=7)	0% (n=0)	8% (n=10)	0.8% (n=1)	0.8% (n=1)	0% (n=0)	12.8% (n=16)	2.4% (n=3)	0% (n=0)	2.4% (n=3)
	2	1.6% (n=2)	2.4% (n=3)	12% (n=15)	0.8% (n=1)	0.8% (n=1)	4.8% (n=6)	0% (n=0)	12.8% (n=16)	0.8% (n=1)	0% (n=0)	0% (n=0)	12.8% (n=16)	6.4% (n=8)	0% (n=0)	8.8% (n=11)
	3	12.8% (n=16)	3.2% (n=4)	32% (n=40)	1.6% (n=2)	0.8% (n=1)	15.2% (n=19)	0.08% (n=1)	20% (n=25)	0% (n=0)	0.8% (n=1)	1.6% (n=2)	19.2% (n=24)	9.6% (n=12)	0% (n=0)	11.2% (n=14)
	4	9.6% (n=12)	6.4% (n=8)	20.8% (n=26)	0.8% (n=1)	0% (n=0)	16.8% (n=21)	0.08% (n=1)	19.2% (n=24)	8% (n=10)	1.6% (n=2)	0.8% (n=1)	17.6% (n=22)	17.6% (n=22)	1.6% (n=2)	12.8% (n=16)
	5	35.2% (n=44)	29.6% (n=37)	12% (n=15)	16% (n=20)	3.2% (n=4)	20.8% (n=26)	2.4% (n=3)	12.8% (n=16)	14.4% (n=18)	6.4% (n=8)	0% (n=0)	25.6% (n=32)	18.4% (n=23)	0% (n=0)	21.6% (n=27)
	6	28% (n=35)	31.2% (n=39)	12.8% (n=16)	16.8% (n=21)	4% (n=5)	25.6% (n=32)	6.4% (n=8)	10.4% (n=13)	16.8% (n=21)	9.6% (n=12)	3.2% (n=4)	8.8% (n=11)	19.2% (n=24)	3.2% (n=4)	12.8% (n=16)
	7	10.4% (n=13)	19.2% (n=24)	3.2% (n=4)	13.6% (n=17)	11.2% (n=14)	9.6% (n=12)	10.4% (n=13)	9.6% (n=12)	21.6% (n=27)	22.4% (n=28)	12.8% (n=16)	1.6% (n=2)	18.4% (n=23)	7.2% (n=9)	17.6% (n=22)
	8	1.6% (n=2)	7.2% (n=9)	% (n=0)	20.8% (n=26)	26.4% (n=33)	1.6% (n=2)	17.6% (n=22)	4.8% (n=6)	24% (n=30)	22.4% (n=28)	17.6% (n=22)	0% (n=0)	5.6% (n=7)	24% (n=30)	4.8% (n=6)
	9	0% (n=0)	0.8% (n=1)	0% (n=0)	19.2% (n=24)	22.4% (n=28)	0% (n=0)	27.2% (n=34)	1.6% (n=2)	8% (n=10)	25% (n=20)	34.4% (n=43)	0% (n=0)	2.4% (n=3)	29.6% (n=37)	5.6% (n=7)
	10	0% (n=0)	0% (n=0)	0% (n=0)	10.4% (n=13)	31.2% (n=39)	0% (n=0)	34.4% (n=43)	0.8% (n=1)	5.6% (n=7)	16% (n=20)	29.6% (n=37)	0% (n=0)	0% (n=0)	34.4% (n=43)	1.6% (n=2)

Table 4. The average total scores given by the groups for each photograph, the average total scores for the 15 photographs, and the comparative statistics of the groups

		Mean	**SD**	**Min.**	**Max.**	**p**
Mean total score for the 15 photographs	Fourth-year dental students	5.78b	1.13	3.67	7.87	0.041*
	Fifth- year dental students	6.56a	0.88	4.40	7.86	
	General dentists	6.31ab	0.98	3.27	8.20	
	Periodontists	6.34ab	0.80	5.40	8.07	
	Orthodontists	6.20ab	0.78	4.27	7.33	
Smile picture 1 (score)	Fourth-year dental students	4.64	1.15	3	7	0.209
	Fifth- year dental students	5.44	1.22	3	7	
	General dentists	5.08	1.41	1	7	
	Periodontists	5.00	1.08	3	6	
	Orthodontists	5.36	1.57	2	8	
	Total	5.10	1.31	1	8	
Smile picture 2 (score)	Fourth-year dental students	5.36	1.41	2	8	0.220
	5th grade students	6.20	1.41	4	9	
	General dentists	5.88	1.33	2	8	
	Periodontists	5.64	1.35	2	8	
	Orthodontists	5.64	0.95	4	8	
	Total	5.74	1.31	2	9	

Smile picture 3 (score)	Fourth-year dental students	3.44	1.71	0	7	0.864
	Fifth- year dental students	3.76	1.69	1	7	
	General dentists	3.64	1.31	2	6	
	Periodontists	3.92	1.38	1	6	
	Orthodontists	3.68	1.60	1	7	
	Total	3.69	1.53	0	7	
Smile picture 4 (score)	Fourth-year dental students	7.12abc#	1.98	3	10	0.015*
	Fifth- year dental students	8.08a	1.57	5	10	
	General dentists	6.56c	1.82	2	10	
	Periodontists	7.76ab	1.69	5	10	
	Orthodontists	6.92bc	1.49	5	9	
	Total	7.29	1.78	2	10	
Smile picture 5 (score)	Fourth-year dental students	9.00a	1.58	5	10	0.017*
	Fifth- year dental students	9.00a	1.70	2	10	
	General dentists	8.44ab	1.71	3	10	
	Periodontists	7.96b	1.30	5	10	
	Orthodontists	7.96b	0.88	6	10	
	Total	8.47	1.52	2	10	
Smile picture 6 (score)	Fourth-year dental students	3.28b	1.69	1	7	0.001*
	Fifth- year dental students	4.84a	1.51	2	8	
	General dentists	4.64a	1.38	1	7	
	Periodontists	5.40a	1.32	3	8	
	Orthodontists	5.12a	1.66	1	7	
	Total	4.66	1.67	1	8	
Smile picture 7 (score)	Fourth-year dental students	7.72b	2.03	3	10	0.011*
	5th grade students	9.04a	1.10	5	10	
	General dentists	8.60ab	1.50	5	10	
	Periodontists	9.00a	1.04	7	10	
	Orthodontists	8.56ab	1.29	6	10	
	Total	8.58	1.49	3	10	
Smile picture 8 (score)	Fourth-year dental students	3.56	2.06	1	8	0.437
	Fifth- year dental students	4.52	1.73	2	9	
	General dentists	4.56	2.08	1	9	
	Periodontists	4.28	2.18	1	8	
	Orthodontists	4.32	2.23	1	10	
	Total	4.25	2.06	1	10	
Smile picture 9 (score)	4th grade students	6.60	1.87	4	10	0.762
	Fifth- year dental students	6.88	1.69	4	10	
	General dentists	6.64	2.09	1	10	
	Periodontists	6.64	1.55	4	10	
	Orthodontists	7.16	1.43	5	10	
	Total	6.78	1.73	1	10	

Smile picture 10 (score)	Fourth-year dental students	7.16	1.37	5	10	0.297
	Fifth- year dental students	7.96	1.79	4	10	
	General dentists	7.88	1.64	3	10	
	Periodontists	8.12	1.66	4	10	
	Orthodontists	7.64	1.86	1	10	
	Total	7.75	1.68	1	10	
Smile picture 11 (score)	Fourth-year dental students	8.24	1.78	3	10	0.351
	Fifth- year dental students	8.96	1.33	4	10	
	General dentists	8.44	1.63	3	10	
	Periodontists	8.68	0.94	7	10	
	Orthodontists	8.84	1.02	6	10	
	Total	8.63	1.38	3	10	
Smile picture 12 (score)	Fourth-year dental students	2.92	1.70	1	7	0.213
	Fifth- year dental students	3.56	1.87	1	6	
	General dentists	3.96	1.76	0	7	
	Periodontists	3.76	1.23	1	6	
	Orthodontsts	3.72	1.51	0	5	
	Total	3.58	1.64	0	7	
Smile picture 13 (score)	Fourth-year dental students	5.08	2.15	1	9	0.376
	Fifth- year dental students	5.76	1.66	2	9	
	General dentists	5.20	1.78	1	9	
	Periodontists	5.08	1.65	2	8	
	Orthodontists	4.72	1.81	1	7	
	Total	5.17	1.82	1	9	
Smile picture 14 (score)	Fourth-year dental students	8.20b	1.52	4	10	0.019*
	Fifth- year dental students	9.36a	1.07	6	10	
	General dentists	8.92ab	1.41	4	10	
	Periodontists	8.76ab	1.01	7	10	
	Orthodontists	8.68ab	0.80	8	10	
	Total	8.78	1.23	4	10	
Smile picture 15 (score)	Fourth-year dental students	4.52b	2.08	1	8	0.044*
	Fifth- year dental students	5.12ab	2.02	1	9	
	General dentists	6.24a	2.47	2	10	
	Periodontists	5.24ab	1.92	1	8	
	Orthodontists	4.76b	1.80	0	7	
	Total	5.18	2.12	0	10	

#: Different lowercase represents statistically significant differences among the groups

Statistically significant difference at *p<0.05

Max; maximum, Min: minimum SD: standard deviation

DISCUSSION

In esthetic smile design, the harmony among the lips, teeth, and gums is considered in its entirety. Nowadays, efforts are made to achieve a dynamic and esthetic smile through minimal invasive procedures for both discrepancies and deficiencies in soft tissues, as well as disorders in the teeth [1,3]. Thus, this study focused on the smile characteristics evaluated by dental specialists including periodontists, orthodontists, general dentists, and dental students, emphasizing their esthetic preferences towards achieving an esthetic smile. Our results show high reliability coefficients across all groups, with the highest rate belonging to the fourth-year students. However, no statistically significant difference was found between general dentists, periodontists, and orthodontists in terms of total score averages whereas the fourth-year students gave significantly lower total score averages compared to the fifth-year students. This leads to partial rejection of our H0 hypothesis.

The smile holds a unique place in an individual's confidence and the structuring of social relationships. Although studies finding no significant difference between SEI values and self-confidence scores have been encountered [12] both physical attractiveness and dentofacial appearance are known to enhance self-confidence [13]. Furthermore, dentofacial appearance can influence not only an individual's popularity but also their perceived social class [14].

Smile design and analysis, a notable part of dentofacial appearance, rely on important concepts in esthetic dentistry. For this purpose, the position, shape, and color of visible elements during a smile are considered valuable concepts for assessment. Concepts important in soft tissue esthetics, such as gum pigmentation, gum growths, and gum deficiencies along with tooth shape and position, tooth deformities, and the facial midline are among the different concepts evaluated in the 10 categories of SEI [5]. Thus, by examining these factors, the esthetic value of a smile, which holds a significant place in facial attractiveness, is provided.

The esthetic value of a smile has been provided in the literature through patient-centered assessments [15] as well as by periodontists [16], orthodontists, general dentists, prosthodontists, and laypeople [9,17]. For this purpose, the visual analog scale (VAS) [18] or the SEI, reported as an objective method [5,6], can be used as possible methods for subjective assessment. However, due to a lack of studies with similar designs to ours, our study results are compared with studies that utilized different methodological analyses of smile esthetics.

In the study by Pham & Nguyen [17], 200 smile images were evaluated by 50 laypersons and 50 professional dentists using VAS. The authors reported that the profession, gender, and age of the evaluators had almost no effect on esthetic perceptions. On the other hand, Gaikwad et al. [9], who assessed smile esthetics and facial attractiveness by evaluating the smile arc and buccal corridors, reported significant differences in ratings among laymen, dentists, and orthodontists, with laymen being less sensitive to these aspects. In our study, all groups consisted of individuals actively involved in patient treatment within the dental profession. Only six out of the 15 evaluated images showed a significant difference among groups. Additionally, no significant difference was found in the total score averages for the 15 images, especially among general dentists, periodontists, and orthodontists, suggesting that these three groups gave similar total average scores to the images. Thus, it can be concluded that actively practicing dentistry fosters esthetic perception, which does not change with specialization.

However, the literature shows variability in the evaluation of various smile esthetic parameters among individuals with different levels of dental education [19]. In our study, fourth-year students were observed to have a significantly lower total score average compared to fifth-year students. Additionally, fourth-year dental students gave lower scores compared to other groups. This outcome might be due to fourth-year students having newly acquiring the experience and knowledge to perceive components that make a difference in smile esthetics. Their cautious approach in esthetic evaluation might also be attributed to their limited clinical experience.

Periodontists are dentists with expertise in soft tissues and have developed perceptions in this area. They play a crucial role in meeting patients' esthetic expectations during smile analysis and in the planning necessary for treatment procedures. Faure-Brac et al. [16] tested their assessments using SEI on videographs with three periodontists. In our study, five groups were tested on photographs. High reliability coefficients were observed across all groups in our study. This indicated that the overall assessment of smile esthetics was very consistent among evaluators, regardless of their prior education.

Among orthodontists, the reliability coefficients were found to be

lower compared to other groups. This may be due to orthodontists not being able to evaluate other factors (such as the buccal corridor and the difference in angles between the commissural line and the occlusal plane) that are not included in SEI but can affect smile esthetics [7]. This is because orthodontists consider balanced and harmonious facial features while evaluating patients with dental and skeletal anomalies.

The limitations of this study include a higher number of female evaluators (71 females) compared to male evaluators (54 males). While some studies have reported that the gender of the evaluator can influence the assessment of smile esthetics [20,21], others have not observed any effect. Future studies should consider the gender variable [17,19,22]. Another limitation is that the smiles were only evaluated statically, without considering video recordings.

CONCLUSIONS

Within the confines of this study, it was observed that the reliability coefficient in the SEI evaluation was high across all groups. Only a total of six out of the fifteen images showed a statistically significant difference among the groups. Moreover, no statistically significant difference was identified in terms of total score averages among periodontists, orthodontists, and general dentists while fourth-year students were observed to give significantly lower total score averages compared to fifth-year students. It can be concluded that actively practicing dentistry fosters the development of esthetic perception, and this outcome does not vary with specialization.

These insights contribute to our understanding of esthetic perceptions in dentistry, suggesting that further exploration into the nuances of esthetic evaluation, including dynamic assessments and gender influences, may provide a more comprehensive understanding of esthetic judgments in dental practice.

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

Informed Consent: Each evaluator voluntarily participated in the study and was thoroughly informed about the purpose and methodology of the study; written consent was obtained from each participant.

Funding: The authors declared that this study has received no financial support.

Acknowledgments: We would like to thank the student dentists, general dentists, periodontists and orthodontists who participated in our study. We are grateful to Prof. Dr. Sıddık Keskin (Van Yuzuncu Yil University, Faculty of Medicine, Department of Biostatistics) for valuable support with statistical analysis. Also, we would like to thank Dr. Murat Tunca for his scientific guidance. (Van Yuzuncu Yil University, Faculty of Dentistry, Department of Orthodontics)

Ethical Approval: The study commenced after approval was obtained from the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (Ethics Number 2023/04-08).

Author Contributions: Conception: D,A; Y,T - Design: D,A; Y,T - Supervision: D,A- Fundings: D,A;Y,T -Materials: D,A; Y,T - Data Collection and/or Processing: D,A; Y,T - Analysis and/or Interpretation: D,A; Y,T - Literature: Y,T - Review: Y,T - Writing: D,A- Critical Review: D-A

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How to Cite;

Altindal D, Tunca Y (2024) A Comparison of the Smile Esthetic Understanding of Periodontists, Orthodontists, General Dentists, and Dental Students. Eur J Ther. 30(3):267-276. https://doi.org/10.58600/eurjther2074

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):277-284.
https://doi.org/10.58600/eurjther2079

Original Research

A Series of Suicides and Homicides by Cyanide in Türkiye: Exploring the Role of Media Reports and the Copycat Effect

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Received: 2024-03-06 **Accepted:** 2024-04-30 **Published Online:** 2024-05-05

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ABSTRACT

Objectives: This paper focuses on the intentional deaths by cyanide that occurred in Türkiye and aims to discuss the effect of internet and the media on these cases.

Methods: Five highly circulated daily newspapers were selected and the term "siyanür", which means "cyanide" in Turkish, were searched within their online search function between 2017-2021. A Google Trends analysis was performed with "siyanür+siyanur" as the keyword, "Türkiye" as the region, and "1/1/2017-12/31/2021" as the custom time range.

Results: Twenty different incidents and news reports of cyanide related suicides and/or homicides with 29 total deaths were found. In Google Trends analysis, seven out of total 8 periods of increased search interest coincided with the news reports related to cyanide deaths.

Conclusions: The authors observed a surge in cyanide-related incidents following a highly publicized case in May 2019, with a peak in November 2019. The study highlights the influence of media coverage on subsequent incidents, with newspapers often using sensational headlines and providing detailed information on suicide methods. Reporting a news article on suicide requires great care and caution. Thus, the guidelines on reporting suicide related news should be implemented nationwide with a collaboration between media professionals and health-care experts.

Keywords: copycat suicide, cyanide, forensic psychiatry, Google Trends, Werther effect

INTRODUCTION

Cyanide has various industrial applications, including gold extraction, metal refining, organic syntheses, and other chemical processes [1, 2]. It can also be found naturally in certain edibles like apple or apricot seeds and bitter almonds [3]. However, it is widely known to be highly toxic to humans. A lethal dose of 0.15-0.3 g/person for potassium cyanide or 0.05 g/person for hydrogen cyanide can rapidly inhibit the electron transportation system in cellular aerobic metabolism. Cyanide poisoning frequently occurs in industrial settings [4]. Additionally, literature reports have documented the use of cyanide for suicidal and homicidal purposes, similar to other toxic substances and drugs [2].

The literature has described the phenomenon of imitation or copycat suicides following widely publicized coverage of a suicide case, known as the "Werther Effect" [5]. This term

originates from Goethe's novel, "The Sorrows of Young Werther," which was banned in several European countries in the 18th century due to its protagonist's suicide. Specific suicide methods, identification with the suicide victim, celebrity suicides, and sensationalized reporting or portrayal of suicide cases contribute to a more "contagious" suicide trend [6]. Numerous studies have investigated this effect in relation to newspaper and television news coverage over the past few decades [7-13]. World Health Organization has issued guidelines for reporting on suicide-related stories [14]. However, the rapid integration of social media and the internet into our lives has facilitated the rapid dissemination of information, which may not adhere to these guidelines and can spread unchecked.

This paper examines homicides and suicides involving cyanide in an 8-month period in Türkiye. Its primary objective is to identify potential future trends, specifically copycat suicide-murder cases, that medical professionals may encounter in their careers. The study investigates the influence of the internet and media on this trend by analyzing online newspaper articles and utilizing Google Trends data.

MATERIALS AND METHODS

Newspaper and Article Selection

According to the official report from the Turkish Statistical Institute in 2020, there were 140 national newspapers in circulation in Türkiye. For this study, the authors selected five highly circulated daily national newspapers: "Hürriyet, Milliyet, Sabah, Sözcü, and Türkiye". These newspapers were chosen based on unofficial online reports, as there are no official statistics on newspaper circulation in Türkiye. The online-only newspapers were excluded in this study, as published newspapers are generally more reliable and professionally moderated.

Main Points;

- The study shows a significant increase in cyanide-related suicides and/or homicides following a sensationalized media coverage.
- Drawing on the concept of "Werther Effect", and utilizing Google Trends data, the paper emphasizes how sensationalized reporting of suicides, may spur copycat incidents.
- The study calls for establishing nationwide guidelines, with collaboration between media professionals and healthcare experts in order to promote accurate and sensitive reporting on suicide and homicide cases.

The selected newspapers, all published in Turkish and available online, were retrospectively reviewed for articles reporting incidents involving deaths from suicides and/or homicides by cyanide exposure between January 2017 and December 2021. The Turkish term "siyanür," meaning "cyanide" in English, was used in the online search function. Duplicate articles were identified and excluded by considering variables such as the date and location of the incident, the person's name, age, and occupation, and other distinct factors. Ultimately, the review process identified 20 distinct events reported in these newspapers, which were related to deaths from suicides and/or homicides by cyanide exposure within the study's reviewed time range.

Google Trends Exploration

Google Trends, introduced by Google in 2004, is a free and publicly accessible tool. It allows users to explore the search frequency of a chosen term or phrase within a specified time range. Researchers have found Google Trends valuable in analyzing population behavior regarding health-related topics, including its potential to predict disease and suicide trends or outbreaks [15-19]. This tool proves particularly advantageous in countries where official health data may not be publicly available. Moreover, it offers benefits over surveys when analyzing sensitive diseases or behavioral topics that could lead to stigmatization, such as AIDS, drug use, and mental illness. By collecting anonymous web search data, Google Trends provides valuable insights.

Google Trends is designed to indicate the popularity of a search term within a specific time frame. It provides data on population-adjusted search volume, meaning that a high number of searches does not necessarily indicate significant search interest if the population size is also large. The output values in Google Trends range from 0 to 100. A value of 0 does not imply zero searches; rather, it suggests that the search volume is too low to be included in the results. On the other hand, a value of 100 represents the peak popularity of the search term within the selected time range.

The authors followed the analytical framework proposed by Mavragani and Ochoa [20] to examine the search interest for the designated terms using Google Trends. The keyword "siyanür" was chosen, with "Türkiye" selected as the region and "1/1/2017-12/31/2021" set as the custom time range, aligning

with the period analyzed in the newspaper study. No specific category was selected for the analysis. To accommodate spelling mistakes and the absence of Turkish letters on some keyboards, the "+" feature was utilized to include "siyanur" and overcome this limitation.

Data Analysis

The data extracted from the news reports included the article date, location of the incident, nature of the event (murder/suicide), gender, age, and the number of victims. This information was recorded in Microsoft Excel for Windows 10 (Microsoft Corporation). To examine potential statistically significant differences in the number of deaths across years, the Chi-Square test was performed using IBM SPSS Statistics v25. A significance level of $p < 0.05$ was employed.

RESULTS

Table 1 provides a summary of the news articles gathered through retrospective review. The study identified a total of 20 different incidents involving cyanide-related suicides and/or homicides, resulting in 29 deaths. The first incident occurred on April 19th, 2017, but the first major incident that generated multiple articles throughout the year was documented in report #8 on May 5th, 2019. This incident marked the beginning of a series of events.

In report #8, a chemistry major deliberately poisoned his family with cyanide mixed drinks, resulting in the death of his parents and hospitalization of one sibling. Over the following eight months, nine more cases with an additional 17 deaths were recorded, with the last incident taking place on January 12th, 2020. Prior to this starting point, there were seven incidents, all of which were suicides, from the beginning of 2017 until January 12th, 2020. From January 12th, 2020, until the end of 2021, only three additional incidents were recorded, all of which were suicides.

The annual death counts related to cyanide exposure, as gathered from the reviewed newspapers, were compared and a statistically significant higher number of reported deaths was found in 2019, with 19 deaths, compared to the other years included in the study ($\chi^2(4) = 38{,}069$, $p < 0.001$).

Figure 1 displays the search output for the terms "siyanür" or "siyanur," which mean "cyanide" in Turkish, using Google Trends. Typically, the selected terms had a value of ≤ 2 during the designated time range. Each surge in search interest for the selected terms with a value higher than "2" is indicated by a letter on top of the corresponding period. Out of a total of 8 periods of increased search interest, 7 coincided with news reports related to cyanide deaths. Only the period of interest "a" did not correlate with any of the reviewed news articles. The highest search interest for the selected terms occurred between November 3rd, 2019, and December 8th, 2019.

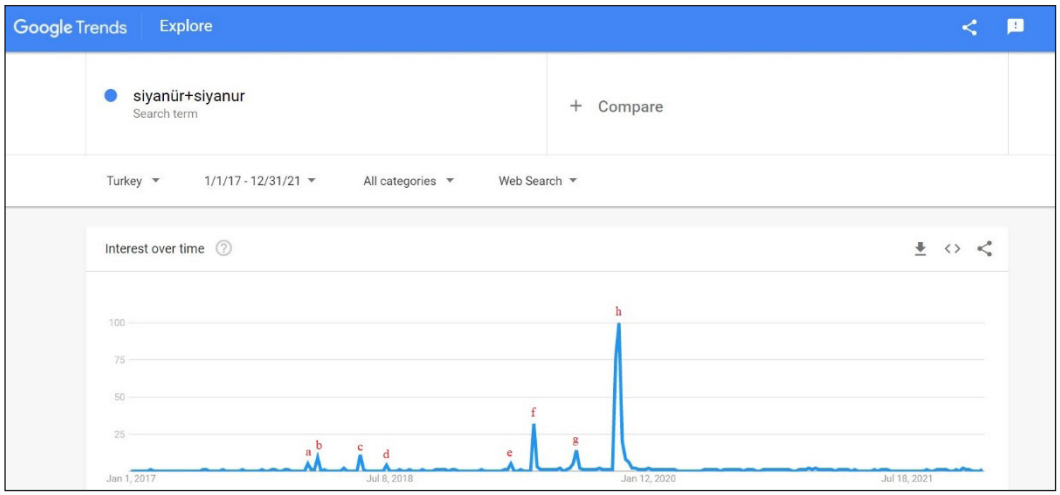

Figure 1. Google Trends analysis for the search term "siyanür+siyanur", which translates into cyanide in Turkish. The periods of increased search interest are each labelled with a letter on top. The start and the end of each period of increased search interest and highest google trends value for each period: **a-** January 14th-21st, 2018 with a value of 5, **b-** February 04th-11th, 2018 with a value of 9, **c-** May 6th-13th, 2018 with a value of 11, **d-** July 1st-8th, 2018 with a value of 4, **e-** March 24th-31st, 2019 with a value of 5, **f-** May 12th-26th, 2019 with a value of 32, **g-** August 4th-18th, 2019 with a value of 14, **h-** November 3rd-December 8th, 2019 with a value of 100

Table 1. A summary of the news-reports that includes the time and location of the incidents, manner of death, sex, age and number of the victims

Report Number	Date (dd/mm/yyyy)	City	Manner of Death	Number of the Victims	Sex and Age (Years) of the Victim
1	19/04/2017	Nigde	Suicide	1	• Male - 19
2	02/11/2017	Diyarbakir	Suicide	1	• Female - 32
3	05/02/2018	Antalya	Suicide	1	• Male - 33
4	09/05/2018	Istanbul	Suicide	1	• Female - 45
5	03/07/2018	Istanbul	Suicide	1	• Female - No data
6	24/11/2018	Ankara	Suicide	1	• Male - No data
7	27/03/2019	Denizli	Suicide	1	• Male - 27
8	16/05/2019	Izmir	Homicide	2	• Male - 46 • Female - 39
9	17/06/2019	Mersin	Suicide	1	• Male - 21
10	14/08/2019	Istanbul	Suicide	1	• Male - 25
11	12/10/2019	Denizli	Suicide	1	• Male - 22
12	06/11/2019	Istanbul	Mass Suicide	4	• Female - 54 • Female - 60 • Male - 48 • Male - 56
13	09/11/2019	Antalya	Homicide-Suicide	4	• Male - 36 (Suicide) • Female - 38 (Homicide) • Male - 5 (Homicide) • Female - 9 (Homicide)
14	15/11/2019	Istanbul	Homicide-Suicide	3	• Male - 38 (Suicide) • Female - 38 (Homicide) • Male - 6 (Homicide)
15	28/11/2019	Antalya	Suicide	1	• Male - 30
16	06/12/2019	Sakarya	Suicide	1	• Male - 21
17	12/01/2020	Van	Suicide	1	• Female - 27
18	16/08/2020	Aydın	Suicide	1	• Female - 30
19	03/11/2021	İstanbul	Suicide	1	• Female - No data
20	17/11/2021	İstanbul	Suicide	1	• Male - 20

DISCUSSION

Cyanide is a highly toxic substance to humans, yet it has been easily accessible in many places, including Türkiye, where it could even be purchased online until recently. Cyanide-related deaths can occur through various means such as injection, inhalation, ingestion, and dermal absorption, and these cases have been extensively documented and reported in the literature. Newspapers have always considered cyanide-related deaths as newsworthy.

During the period from January 2017 to May 2019, the authors of the study encountered a total of 7 separate incidents of cyanide poisoning reported in the reviewed articles. However, a significant increase in such incidents occurred after a chemist murdered his parents with cyanide mixed drinks in Izmir on May 16th, 2019. This event received extensive coverage in the news with sensational headlines, leading to a series of deaths over the subsequent eight months, resulting in a total of 10 incidents and

19 deaths. The peak of this trend occurred in November 2019, with four different incidents related to cyanide poisoning and a total of 12 deaths within a single month.

Coinciding with this peak trend, the Turkish government took action by implementing strict regulations on the sale of cyanide, including limiting its availability to the public and making online sales of cyanide compounds illegal. Following the last incident in this eight-month period on January 12th, 2020, and the prohibition of online cyanide sales, only three news reports dealing with similar incidents were noticed until the end of 2021.

The series of deaths in 2019, along with the significantly lower number of deaths in the years before and after, prompted the authors of the article to investigate whether the Werther effect, which refers to imitation or copycat suicides after highly publicized suicide cases, played a role in these events.

While suicides can be influenced by various factors, including mental health problems and social factors, one important area of research examines the potential impact of media stories on subsequent suicidal behavior [5]. The rapid advancement of technology, the internet, and social media has significantly enhanced communication in recent decades. Electronic media, in particular, can be more concerning than print media due to its ability to reach a larger population. However, it is important to note that the study being referred to predates the widespread use of the internet and social media platforms, which means that news stories can now reach an even larger and more vulnerable population.

It is speculated that various forms of media, such as news stories, books, movies, or video games, can potentially lead to copycat suicide or murder cases within a population. Individual, demographic, media-related, and cultural factors can all play a role in whether someone mimics the behaviors they see in the media. Examples of such factors include age, sex, mental state, personality, substance abuse, socioeconomic status, and the media's attention to and language used in a particular story. Research suggests that young individuals and those with previous suicidal thoughts or attempts may be more vulnerable to suggestion or the "Werther effect" triggered by news reports [21-24]. With the ease of accessing information worldwide, it is possible that the incidence of copycat crimes or suicides may increase in the future.

In recognition of the potential harm caused by irresponsible reporting, World Health Organization (WHO) has published guidelines [14] for media professionals on reporting suicide-related news stories. These guidelines, last updated in 2017, explicitly state that media professionals should avoid repetitive stories about suicide, sensational language or headlines, and detailed descriptions of suicide methods or locations. However, in the newspaper review conducted by the authors of the present study, it was observed that most of the news articles used sensational headlines and provided detailed descriptions of suicide methods. Some of the incidents were repeatedly highlighted in newspaper articles over a span of several months, specifically incidents #8, #12, #13, and #14. This repetitive coverage may have contributed to the prolonged exposure of these incidents to the public. Furthermore, it is worth noting that all of the articles were easily shareable through social media platforms, which could have potentially amplified their reach and impact.

However, despite the wide dissemination of these articles, none of them were effectively utilized to promote suicide prevention or provide information on where individuals could seek help. This missed opportunity to raise awareness about available support and resources for those in need reflects a gap in the responsible reporting of suicide-related news.

It has been proposed that the influence of the copycat effect may vary across different regions due to variations in the implementation of international guidelines on reporting suicide [21]. In the present study, it was evident that the newspapers reviewed did not adhere to the WHO guidelines on reporting suicide. This finding aligns with the results of another study conducted in Türkiye, which also highlighted the inadequate implementation of these guidelines in suicide-related news reports [25].

Furthermore, in a separate study analyzing news reports of 11 cases related to cyanide deaths between January 2018 and December 2019 (which are also included in the present study), it was discovered that detailed information about suicide notes was provided in 9 out of 11 cases, explicit discussions about the cause of death were present in 5 cases, and the method of obtaining cyanide was clearly stated in all cases [26]. These findings underscore the lack of responsible reporting practices observed in the coverage of cyanide-related incidents.

In the field of medical literature, there is extensive discussion about the potential role of unregulated media reports in suicide contagion. Research by Niederkrotenthaler et al. [27] introduced the concept of the "Papageno effect," suggesting that media reports on suicidal ideation without accompanying suicide attempts or completed suicides can have a preventive effect. The main finding highlighted by the authors was that such articles may positively impact individuals with suicidal tendencies by creating empathy and offering a sense of hope, as they read about others who continue to live. Importantly, these types of reports constituted only a small proportion (8.8%) of the news reports in their study, further emphasizing the importance of the wording used in suicide-related articles.

While many studies on the Werther effect have focused on celebrity suicides, the present study supports the hypothesis that non-celebrity suicide-related news can also influence copycat suicide cases [28, 29]. In the current study, the authors attended the autopsies of five cases reported in two different news articles, and detailed crime scene investigations revealed suicide notes warning others about cyanide. This indicates that the individuals who carried out these acts were aware of the effects of cyanide exposure and had conducted preliminary research on the substance. The high demand for information on cyanide during this period, as indicated by Google Trends analysis, may have resulted in increased availability of online information on cyanide, including not only its effects but also information on how and where to obtain it. Given that cyanide ingestion as a method of suicide is relatively uncommon and unconventional, the cases in the present study can be considered as potential copycat suicides.

As previously mentioned, all the news reports reviewed in this study were easily shareable on social media platforms, as they included share buttons for popular platforms. The Google Trends analysis revealed a surge in search interest related to cyanide after each news report on a death by cyanide poisoning. The first significant increase in search interest occurred with report #8, which contained sensational and newsworthy details. The search interest reached its highest point in November 2019, coinciding with the peak of cyanide-related suicides and/or homicides. These news reports, starting from report #8 until the end of the year, likely reached millions of people across the country, contributing to the series of events related to cyanide in Türkiye during the latter half of 2019. It is important to note that all these news reports had unregulated content without adhering to the guidelines set by the WHO.

The Google Trends analysis showed that seven out of eight periods of increased search interest correlated with news reports on cyanide-related deaths. The only period that didn't correlate with any reviewed news article was associated with a celebrity homicide case, where the perpetrator's search history included the term "siyanür." The news story also contained extensive information on cyanide, its effects, and its uses, which the authors considered unnecessary and in violation of international guidelines. This anecdote further supports the importance of regulating news reports according to guidelines. It is also essential to periodically educate journalists on reporting suicide and homicide-related news. The arguments presented in this study do not advocate for media censorship. Instead, the authors emphasize the need for careful reporting on sensitive topics and the potential impact these reports can have, positive or negative, on vulnerable individuals. To ensure positive outcomes and responsible reporting, media professionals and healthcare professionals should collaborate and establish a framework that implements international guidelines for safe news reporting.

Limitations

While Google Trends provides valuable insights into search interest, it does not represent actual behavior or motivations behind searches. Additionally, the study design is observational, and therefore, causal relationships cannot be inferred from the findings. While the study suggests a potential association between media coverage and cyanide-related suicides and homicides, other confounding variables and underlying factors may contribute to these events.

CONCLUSION

This paper highlights the importance of medical professionals staying informed about emerging trends worldwide. In the age of the internet, information spreads rapidly, and what was once an isolated incident can quickly become a new trend. The media, whether print or online, can be both a powerful tool and a potential risk factor in influencing suicide rates and copycat behavior. The writing style and content of news articles on suicide play a crucial role in determining their impact. Careful and cautious reporting is necessary to minimize the risk of negative outcomes and maximize the potential for prevention.

In order to achieve this level of care and caution, it is essential to implement nationwide guidelines on reporting suicide-related

news. This requires collaboration between media professionals and healthcare experts who can provide guidance and expertise. Continuous education of journalists on responsible reporting of suicide is also vital. By working together and fostering a framework that promotes safe reporting practices, media professionals can contribute to suicide prevention efforts and help individuals struggling with suicidal ideations cope more effectively.

Acknowledgment
During the preparation of this work, the authors used an artificial intelligence tool, QuillBot, in order to check the grammar and the academic language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Competing Interests: The authors declare that they have no competing interests.

Funding: No funding was received for this study.

Ethical Statement: As the data and incidents include previously reported news articles, and all the information is available online, formal ethical clearance was not considered.

Authors' contributions: CD reviewed, analyzed, and interpreted the data, wrote the drafted manuscript. MA corrected, organized, and approved the final manuscript.

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How to Cite;

Deveci C, Atılgan M (2024) A Series of Suicides and Homicides by Cyanide in Türkiye: Exploring the Role of Media Reports and the Copycat Effect. Eur J Ther. 30(3):277-284. https://doi.org/10.58600/eurjther2079

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):285-291.
https://doi.org/10.58600/eurjther2081

Original Research

Evaluation of Patients with Postoperative Pancreatic Fistula After Isolated Splenectomy: A Retrospective Study

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Received: 2024-03-06 **Accepted:** 2024-05-09 **Published Online:** 2024-05-13

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ABSTRACT

Objective: Postoperative pancreatic fistula (POPF) is a potentially life-threatening complication. This complication occurs not only after pancreatic surgery but may also arise after other abdominal procedures. In this study, we aimed to determine the incidence and risk factors of POPF in patients undergoing isolated splenectomy.

Methods: Patients who underwent isolated splenectomy were identified. POPF was defined according to the 2016 update of International Study Group of Pancreatic Fistula classification and graded as biochemical leak (BL), grade B fistula, and grade C fistula. Characteristics and perioperative variables were compared between patients who had pancreatic fistula and those who have not.

Results: The study cohort consisted of 59 patients with median age 38.9 years, and 50.8% male. The indication was trauma in 18 (30.5%) patients. Twenty (33.9%) patients were operated upon emergently. Thirty-seven (62.7%) splenectomies were performed open. Out of all patients, 14 (23.7%) developed any sort of pancreatic fistula. BL occurred in 11 (18.6%) patients and 3 (5.1%) patients developed a grade B fistula. Comparison of patients with and without BL/POPF demonstrated no significant differences in demographics, surgical indication, operative method, surgical approach, or postoperative outcome.

Conclusions: Despite higher incidence of pancreatic leak, the rate of clinically relevant fistula is relatively low. In this study, we did not identify any factors associated with BL/POPF. Thus, further studies are needed on pancreatic fistula after splenectomy.

Keywords: complication, drainage, pancreatic fistula, splenectomy

INTRODUCTION

Splenectomy is performed for a variety of indications, such as an emergency procedure following trauma and the diagnosis and treatment of hematological disorders in elective settings. Recently, with the development of laparoscopic instruments, surgical techniques, and advancing technology, laparoscopic splenectomy has been widely applied as a standard procedure for splenic surgery [1,2]. In the emergency setting, open splenectomy is the most commonly performed procedure [3]. Due to the anatomical proximity of the spleen to the pancreas

tail, mobilization of the spleen increases the risk of pancreatic injury and fistula [4].

Postoperative pancreatic fistula (POPF) is a serious complication after pancreas surgery and is associated with an increased risk of poor outcomes. This potentially life-threatening complication occurs not only after pancreatic resection but may also occur after other abdominal procedures, such as gastrectomy and splenectomy [5-7]. POPF prevalence after splenectomy ranges from 4.5% to 16%, some of which may have important clinical implications [5,6]. Despite well-established indications for performing splenectomy and approaches to managing splenic disorders, only limited data are available regarding pancreatic complications, especially POPF, after splenectomy. In this study, we aimed to determine the incidence of POPF in patients undergoing isolated splenectomy and to compare patients with and without POPF regarding clinical features.

MATERIALS AND METHODS

Study Design and Study Population

Following institutional review board approval from the Ethics Committee of Gulhane Training and Research Hospital (2022/15), we performed a single-center retrospective analysis of patients undergoing splenectomy between January 2016 and December 2022. Patients who underwent a splenectomy during another abdominal procedure, those who underwent multiple organ resections due to malignancy, or underwent any organ removal, resection, or repair other than a splenectomy after traumatic injuries were excluded from the study. We also excluded those patients who underwent partial splenectomy, patients younger than 18 years at initial presentation, patients without surgical drains, and patients with missing data (Figure 1).

Main Points;

- Splenectomy carries the potential risk of complications, either during surgery or in the postoperative period.
- Postoperative pancreatic fistula (POPF), which is also a major complication of splenectomy, is associated with a higher risk of unfavorable outcome.
- Notwithstanding the higher incidence of pancreatic leak (23.7%), the rate of clinically relevant fistula is comparatively low (5.1%) in this study.
- No factors were identified that were associated with biochemical leak or POPF. Consequently, further studies are required to elucidate the relationship between pancreatic complications and splenectomy.

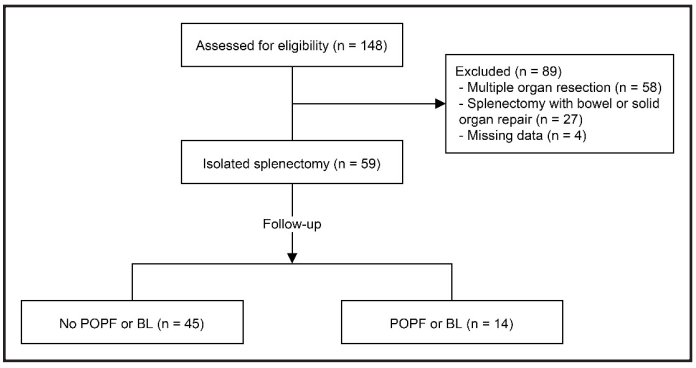

Figure 1. CONSORT flow diagram of study enrolment, allocation, follow-up, and analysis.

Data Collection

Data collected included patient characteristics, indication for splenectomy (trauma or non-traumatic), surgical procedure (elective or emergency), surgical approach (open or laparoscopic), spleen weight, length of hospital and intensive care unit stay, and 30-day outcomes.

Outcome Variables

The primary outcome of interest was the development of a postoperative BL or pancreatic fistula after splenectomy. POPF was defined according to the 2016 update of International Study Group of Pancreatic Fistula (ISGPF) classification [8]. While pancreatic leak which has no clinical impact on the patient's hospital course was defined as BL (formerly grade A POPF), grade B and grade C POPFs were considered clinically relevant fistulas. The Clavien–Dindo classification was used to grade complications [9]. Clinical characteristics and perioperative variables were compared between patients who had BL or POPF and those who had not.

Statistical Analysis

Examinations of normal distribution assumptions for continuous data were assessed with quantile-quantile plots, histograms, and the Shapiro-Wilk test. Categorical data were presented as number (n) and percentage (%), and continuous data as median with range values. Associations between variables were evaluated using the Wilcoxon Mann Whitney U test (for continuous variables) and the Pearson χ^2 or Fisher exact tests (for categorical variables),

where appropriate. All tests were two-sided, and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using Jamovi, version 2.3.2.0 (The Jamovi project, Sydney, Australia) [10].

RESULTS

Of the 148 patients who underwent a splenectomy, the records of 59 patients were analyzed in this study after excluding patients who had multiple organ resections (n = 58), patients undergoing splenectomy with any bowel or solid organ repair (n = 27), and patients with missing data (n = 4) (Figure 1). The median age was 38.9 (range, 19.1–76.9) years, and 50.8% were male. The indications for splenectomy were trauma (30.5%), immune thrombocytopenia (ITP) (18.6%), splenic mass (18.6%), hypersplenism (13.6%), autoimmune hemolytic anemia (5.1%), lymphoma (5.1%), hereditary spherocytosis (1.7%), splenic abscess (3.4%), and splenic hydatid cyst (1.7%). 22 (37.3%) cases were completed laparoscopically, 4 (6.8%) were converted to open surgery, and 33 (55.9%) splenectomies were performed open.

Out of all patients, 14 (23.7%) developed any sort of pancreatic leak. A BL occurred in 11 (18.6%) patients, whereas 3 (5.1%) patients developed a grade B fistula. There were no patients with grade C fistula. Table 1 presents a comparison between patients who underwent isolated splenectomy having pancreatic fistula or BL and patients without any sort of POPF regarding demographic and clinical data. Comparison of the two groups demonstrated no significant differences in age, gender, surgical indication, operative method, surgical approach, and postoperative short-term outcomes. Not surprisingly, the rate of discharge with a drain was significantly higher in patients with BL or POPF than in those without a pancreatic leak (28.6% versus 6.6%, p = 0.026).

In the subgroup analysis, when compared to BL, patients with grade B fistula had a longer length of hospitalization (8.2 days versus 32.3 days, p = 0.046). In addition, patients who underwent emergency splenectomy because of a traumatic injury had a higher rate of grade B fistula (p = 0.031). There were no significant differences between patients with BL and patients with grade B fistula regarding demographic variables, other perioperative data, and postoperative outcomes.

Table 1. Comparison of patients having biochemical leak or postoperative pancreatic fistula and patients without any leaks

	Non-POPF/ BL (n = 45)	POPF or BL (n = 14)	p
Age, years	39.5 (19.1–76.9)	30.5 (20.2–73.8)	0.318
Male gender, n (%)	22 (48.9%)	8 (57.1%)	0.590
Indication for splenectomy, n (%)			0.516
Non-trauma indications	30 (66.7%)	11 (78.6%)	
Trauma	15 (33.3%)	3 (21.4%)	
Operative method, n (%)			0.342
Elective	28 (62.2%)	11 (78.6%)	
Emergency	17 (37.8%)	3 (21.4%)	
Surgical approach, n (%)			0.260
Open	30 (66.7%)	7 (50.0%)	
Laparoscopic	15 (33.3%)	7 (50.0%)	
Spleen weight, g	216 (110–4000)	250 (160–2330)	0.497
ICU stay, n (%)	29 (64.4%)	10 (71.4%)	0.753
Length of hospital stay, days	6 (2–24)	8 (3–63)	0.316
Discharge with drain, n (%)	3 (6.6%)	4 (28.6%)	0.026
Postoperative 30-day complication, n (%)†	4 (8.9%)	2 (14.3%)	0.559

BL, biochemical leak; ICU, intensive care unit; POPF, postoperative pancreatic fistula

† postoperative ≥ grade 3a complications other than pancreatic fistula

DISCUSSION

Splenectomy is a commonly performed procedure in general surgical practice [3,4,11]. While splenectomy can be performed as a multi-organ resection during another abdominal procedure due to malignancy or trauma, it can also be performed as an isolated procedure in patients with trauma or those with hematological disorders [1,2]. Regardless of the surgical technique performed, it carries the potential risk of complications, either during surgery or in the postoperative period [12,13]. Although splenectomy remains a frequently performed procedure, studies on pancreatic complications after splenectomy are limited. Especially, the incidence of POPF after isolated splenectomy and the effects of pancreatic fistula on short-term clinical outcomes is unclear [2,5-7]. This single-center retrospective study showed that pancreatic leak is not a rare complication and occurs in 23.7% of patients

undergoing isolated splenectomy. In the present study, most pancreatic leaks were BL with no clinical impact on patients' short-term outcomes

Splenectomy is an independent risk factor for POPF in patients who have had a gastrectomy or those undergoing multiple resections such as cytoreductive surgery [14-16]. It is also well known that POPF occurs more often in patients who have undergone splenectomy for oncological indications or technical difficulties during the course of other surgical procedures [5]. With the realization that there is limited data, this study focused on the incidence and clinical outcomes of POPF, especially in patients who underwent isolated splenectomy. In addition, to evaluate the true incidence of the pancreatic leak, especially BL, we only included in the study patients who had an operatively placed drain after splenectomy. In a recent study evaluating POPF after splenectomy with multi-organ resection, traumatic splenectomy, and isolated splenectomy, the incidence of POPF was reported as 14.6% [5]. Because surgical drains were placed according to surgeons' preference, there is no information in this study about how many patients had a drain placed. Therefore, the low incidence of POPF may be due to the comparatively rare use of intraperitoneal drains, especially in patients who underwent an elective isolated splenectomy. In another study, the total incidence of clinically relevant POPF was reported to be 4.2% [7]. However, in contrast to this study, we included BL in the analysis and hence report a higher rate of pancreatic fistula. When excluding BL to focus entirely on grade B and grade C fistula, we found an incidence of 5.1%, which is comparable to rates reported in the literature [2,5-7,17].

In the present study, comparison of patients with and without BL/POPF following isolated splenectomy demonstrated no significant differences in demographic variables, surgical indication, operative method, surgical approach, and postoperative short-term outcomes. One of the rare studies that investigated the risk factors for POPF after splenectomy showed that secondary splenectomy (splenectomy for other organ pathologies or technical reasons) and the use of energy-based devices were to be independent risk factors in multivariate analysis [5]. In a recent study investigating 167 patients who underwent splenectomy due to hepatolenticular degeneration and hypersplenism, degree of splenomegaly, pancreatic texture, and operative method were found to be independently associated with POPF [7].

Laparoscopic splenectomy is a safe procedure and has a low complication rate [2,4,12,18]. Up to 15% of laparoscopic splenectomies have has reported pancreatic complications (either an isolated hyperamylasemia or a pancreatic injury) [2]. However, the true impact of surgical approach on the incidence of the pancreatic fistula is unclear [12]. Due to the close contact of the splenic hilum with the pancreatic tail, intraoperative trauma of the pancreas during dissection of the splenic hilum may cause POPF [19]. In a meta-analysis that evaluated the clinical efficacy of surgical technique (laparoscopic or open) in the treatment of ITP, it was not found a significant difference in the incidence of pancreatic fistula between laparoscopic and open splenectomy [17]. In the present study, BL/POPF was found to be higher in laparoscopic splenectomy, but there was no statistical difference compared with the open group (31.8% versus 18.9%, $p = 0.260$). Other factors that might play a role in POPF are the operative setting (elective or emergency) and splenic hilum ligation technique. Emergency splenectomies, including patients who had trauma and patients who underwent additional abdominal procedures or multiple resections, are associated with higher postoperative complications and mortality rates [20]. In our study, no statistically significant difference was determined between elective and emergency splenectomy in respect of BL/POPF rate (28.2% versus 15.0%, $p = 0.342$). This result is similar to that reported by Mehdorn et al. [5] using both univariate and multivariate analyses. However, in the subgroup analysis, compared to elective splenectomy, patients who underwent emergency splenectomy because of a traumatic injury had a higher rate of grade B fistula. During splenectomy, there are various techniques used to ligate splenic vessels such as sutures, staples, clips, ultrasonic shears, and bipolar-sealing devices. There is no splenic hilum ligation technique that has been proven to reduce POPF development [21].

There is conflicting evidence in studies evaluating the relationship between splenomegaly and postoperative complications. While in a study by Targarona et al.[22], multivariate analysis revealed that spleen weight was a predictive factor for complications, Rodríguez-Luna et al. [23] and Alobuia et al. [24] did not find an association between spleen size and postoperative complications. Similarly, we could not show an influence of spleen weight on the development of BL/POPF.

Despite the higher incidence of pancreatic leaks, the rate of clinically relevant POPF is relatively low. Therefore, in recent studies, BL (formerly grade A POPF) is no longer considered to be a true pancreatic fistula or complication [8]. Moreover,

detection of BL is also only possible when a drain is placed. When surgeons do not place a surgical drain at the time of splenectomy, the presence of increased amylase levels in the abdominal fluid is not even detected [8,25]. A recently published evidence-based guideline from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) suggests that selective drain placement should be considered instead of routine placement based on patient- or procedure-related factors during minimally invasive splenectomy [11]. In a prospective study aiming to evaluate risk factors and effective prophylactic treatment strategies for preventing the development of pancreatic fistula after laparoscopic splenectomy in patients with hypersplenism due to liver cirrhosis, it was found that combined use of fibrin glue and polyglycolic acid (PGA) felt on the staple line and dissected area after laparoscopic splenectomy reduced pancreatic fistula [6]. In this study, which used a routine closed suction drain after laparoscopic splenectomy, while 21.7% of patients who used a fibrin sheet after the operation presented with pancreatic fistula, patients using PGA felt and fibrin glue had not experienced any cases of pancreatic fistula. In addition, the authors emphasized the importance of prophylactic strategies to reduce pancreatic fistula after splenectomy for patients at high risk. However, neither the present study nor the study mentioned above could identify a predictive factor of POPF after splenectomy from the patients' demographic variables and clinical characteristics.

Limitations

There are several limitations to this study, which should be highlighted. This is a retrospective analysis and is subject to all potential biases associated with such an approach. It was carried out in a single center, limiting the generalizability of our findings. In addition, the number of patients in the present study was relatively low because of strict inclusion criteria aiming to evaluate the true incidence of POPF. Despite these limitations, this study provides evidence for the understanding and identification of the true incidence of POPF after isolated splenectomy and presents clinical outcomes of patients with and without pancreatic fistula.

CONCLUSION

Pancreatic fistula is a potentially life-threatening and morbidity-increasing complication. It is important to identify factors that can be addressed perioperatively to reduce the possibility of POPF and to ensure optimal clinical outcomes in patients undergoing splenectomy. While there are various risk factors for the development of POPF, we did not identify any factor associated with BL/POPF after isolated splenectomy. Thus, further studies are needed on pancreatic complications after splenectomy.

Declaration of conflicting interest: The authors declare that there is no conflict of interest.

Funding: The authors declared that this study has received no financial support.

Authorship: All authors had access to the relevant data and a role in writing the manuscript.

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Gulhane Training and Research Hospital (approval no: 2022/15).

Author Contributions

Conception: SUC, MBD, YG, HEP, MMH, MO, SAK; Design: SUC, SAK; Supervision: SUC, SAK; Fundings:SUC, SAK; Materials: SUC, MBD, YG, HEP, MMH, MO, SAK; Data Collection and/or Processing: MBD, YG, HEP, MMH, MO; Analysis and/or Interpretation: SUC, SAK; Literature Review: SUC, MBD, YG, HEP, MMH, MO, SAK; Writing: SUC, MBD, YG, HEP, MMH, MO, SAK; Critical Review: SUC, MBD, YG, HEP, MMH, MO, SAK.

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How to Cite;

Celik S, Demir MB, Gulap Y, Polat HE, Hidiroglu MM, Ozkara M, Kesikli SA (2024) Evaluation of Patients with Postoperative Pancreatic Fistula After Isolated Splenectomy: A Retrospective Study. Eur J Ther. 30(3):285-291. https://doi.org/10.58600/eurjther2081

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):292-302.
https://doi.org/10.58600/eurjther2090

Original Research

New Biomarker Candidates of Sepsis: Diagnostic and Prognostic Value of Presepsin, Angiopoietin 1 and 2

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Received: 2024-03-13 **Accepted**: 2024-05-06 **Published Online:** 2024-05-07

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ABSTRACT

Objective: Sepsis is an uncontrolled inflamatory response that occurs in the body towards infection. It's an important clinical picture that is seen in high morbidity and mortality so early diagnose and treatment areimportant. For that reason, for the septic cases to get early diagnosis and to predict the prognosis, new biomarkers are needed nowadays. Presepsin, angiopoietin 1 and angiopoietin II are biomarkers that are not usedroutinely yet, in our study, according to the new description given in Sepsis 3 meeting, in cases that are diagnosed with sepsis, we aimed at comparing diagnostic and prognostic values of these biomarkers.

Methods: In our study, there were two groups. Patient group consisting of 48 cases with 33 men and 15 women and control group consisting of 42 cases with 23 men and 19 women. Control group is selected within patient relatives with similarities of age and sex. Demographic datas, accompanying diseases, APACHE II, SAPS and SOFA scores counted in the first 24 hours, leukocyte count, eritrocyte sedimentation rate, C-reactive protein, procalcitonin value, culture sampling results (blood, urine, sputum, endotracheal aspirate) that are measured in their stays, 7th and 28th day mortality counts after their ICU stays are written down. Presepsin, angiopoietin I and angiopoietin II are detected by sandwich ELISA method.

Results: According to demographic features there isn't any significant statistical difference between the patient group and the control group ($p>0.005$). In patient group Presepsin, angiopoietin I and angiopoietin II values were statistically high significantly compared to the control group ($p<0.001$). After the evaluation, serumpresepsin value noticed that has a diagnostic value in the diagnosis of sepsis (EAA: 0.74, 95%GA: 0.64–0.85, $p<0.001$). The suggested border value for this value is predicted as 0.47, 73%sensitivity and 62% specificity are determined. Serum angiopoietin I value noticed that has a diagnostic value in the diagnosis of sepsis (EAA: 0.80, 95%GA: 0.71–0.89, $p<0.001$). The suggested border value for this value is predicted as 178.24, 69% sensitivity and 69% specificity are determined. Serum angiopoietin II value noticed that has a diagnostic value in the diagnosis of sepsis (EAA: 0.89, 95% GA: 0.82–0.95, $p<0.001$). The suggested border value for this value is predicted as 77.56, 84% sensitivity and 83% specificity are determined.

Conclusions: In our study, presepsin, angiopoietin I and angiopoietin II values are determined as statistically high according to healthy control group and are found successful with high sensitivity and specificity in diagnosing. Presepsin, angiopoietin I and angiopoietin II values in septic patients are found successful with high sensitivity and specificity at 7th and 28th days mortality prediction.

Keywords: Sepsis, Presepsin, Angiopoitein I, Angiopoitein II

INTRODUCTION

Sepsis is a syndrome in which physiological, biological and biochemical abnormalities occur as a result of the body's uncontrolled inflammatory response to infection, and although the incidence of diagnosis is increasing, it continues to have high morbidity and mortality due to its complex pathophysiological mechanisms and difficulty in treatment [1,2].

Sepsis is seen in millions of patients every year around the world, and 25% (perhaps more) of patients die because of this. Early initiation of appropriate treatment affects prognosis and mortality in many causes of sepsis, such as trauma, acute myocardial infarction, and ischemic cerebrovascular events. Therefore, it is vital for the physician to recognize sepsis in time [3].

It has been determined that the percentage of sepsis resulting in mortality varies in different studies. Mortality increases when the etiology of sepsis includes advanced age, comorbid diseases, immunosuppression, major trauma, burns, interventional procedures such as catheter insertion during intensive care stay, and hemodialysis.

Inflammatory reactions in sepsis involve humoral, cellular or molecular pathways. As a result of systemic inflammation, some changes are observed in body temperature, leukocyte count, heart rate, respiratory rate and blood pressure. These changes are neither specific nor sensitive for sepsis [4]. Due to technological developments, in recent years, in addition to these criteria, procalcitonin, tumor necrosis factor-α (TNF-α), interleukin-1beta (IL-1β), interleukin-6 (IL- 6) and interleukin-8 (IL- 8). The use of bioactive molecules such as cytokines, presepsin, angiopoietin 1 (Ang 1), angiopoietin 2 (Ang 2) has been suggested. A few of these have come into use, and research continues for some of them.

Main Points;

Our study investigates alternative markers that can be used in the diagnosis of sepsis, which is an insidious but fatal disease. Sepsis is tried to be diagnosed clinically by qSOFA classification with examination findings such as tachypnea, tachycardia and low blood pressure, which occur as a result of multisystemic dysfunction as a result of exaggerated immune response to foreign microorganisms. In addition, pathogen detection is made from samples taken from various body tissues. However, the diagnosis of sepsis is delayed due to the emergence of the specified clinical findings after various pathogens, especially bacteremia, circulate in the tissues and cause infective mechanisms. In this study, the diagnostic properties of presepsin and angiopoietin 1 and 2 were investigated in patients diagnosed with sepsis.

Although current biomarkers show great promise in indicating the severity of sepsis, the highly variable and nonspecific nature of the signs and symptoms of sepsis make the prospect of a single biomarker classification less valuable. Nowadays, it is of great importance to identify biomarkers and combine them with clinical scoring systems for risk stratification and assessment of prognosis of sepsis.

MATERIALS AND METHODS

Aim of Work

In our study, we examine whether the levels of cytokines that play a role in the pathogenesis of sepsis correlate with the diagnostic value and disease activity of newly discovered sepsis biomarkers.

Study Design and Population

The study was started with the decision of Gaziantep University Faculty of Medicine Clinical Research Board dated 17.04.2019. This study was supported by Gaziantep University Scientific Research Projects with project number TF.UT.19.29. The study was conducted prospectively with patients with sepsis who were admitted to the Intensive Care Unit of Gaziantep University Faculty of Medicine, Department of Internal Medicine, between may and august 2019.

Lab Investigations

1. Volunteer patients who were diagnosed with sepsis according to the definitions determined at the Sepsis 3 meeting of the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM), whose stay in intensive care lasted longer than 24 hours, who were over 18 years old, and whose informed consent form was signed by the patient or their relatives, were included.Patients with any known inflammatory disease or active malignancy history were not included in the study.
2. In our study, the control group consisted of a total of 42 cases, 23 of whom were men and 19 of whom were women, while

the patient group consisted of a total of 48 cases, of which 33 were men and 15 were women. Control group cases were selected from the patient group and their relatives who were similar in terms of age and gender.

3. APACHE II, SAPS and SOFA score values, which are among the intensive care scoring systems that show the severity of the disease, were used in the patient group. APACHE II, SAPS and SOFA scores of the patients included in the study were calculated using the parameters analyzed in the first 24 hours after their admission to the intensive care unit.
4. Demographic data of the patients, comorbidities, APACHE II, SAPS and SOFA scores calculated in the first 24 hours of admission, leukocyte count measured on the day of admission, erythrocyte sedimentation rate, C-reactive protein, procalcitonin values, culture test results (blood, urine, sputum, endotracheal aspirate), mortality numbers on the 7th and 28th days after intensive care admission were recorded.
5. The blood sent to the laboratory for analysis of routine examinations was kept for 30 minutes and then centrifuged at 3500 rpm for 15 minutes. After centrifugation, patient serums were placed in Epandorf tubes and stored at -80C until the study day for analysis of presepsin, angiopoietin 1 and angiopoietin 2 tests.
6. Presepsin, angiopoietin 1 and angiopoietin 2 levels were determined by the sandwich-ELISA method.

Statistical Analysis

All analyzes were performed using the Statistical Package for the SocialSciences software version 24.00 (SPSS Inc., USA). Descriptive values are expressed as number (n) ± standard deviation. Since continuous variables did not comply with normal distribution according to the normality assessment made with Kolmogrov-Smirnov and Shapiro-Wilk tests, the nonparametric test was compared with the Mann-Whitney U test. The relationship between variables was evaluated with the Spearmen Correlation Test. The relationship status according to the correlation coefficient is presented in Table 1. The decision-making properties of the measurement values in diagnosing sepsis and their prognosis predictive power were examined by Reveiver Operating Characteristics (ROC) curve analysis. In the presence of significant limit values, the sensitivity and specificity values of these limits were calculated. Statistical significance level was accepted as $p<0.05$ for all tests performed.

RESULTS

Demographic characteristics of the patient and control groups, intensive care scoring systems, levels of acute phase reactants during hospitalization and statistical significance levels are shown in Table 2. No statistically significant difference was determined between the patient and control groups in terms of demographic characteristics ($p>0.05$).

Serum presepsin, angiopoietin 1 and angiopoietin 2 levels and significance levels of the patient and control groups are shown in Table 3. Presepsin, angiopoietin 1 and angiopoietin 2 levels in the patient group were determined to be statistically significantly higher than in the control group ($p<0.001$).

Table 2. Demographic Comparison of Patient and Control Group

	Patiens(48)	Control(42)	p
Age	68(21/93)	68(44/85)	0.639
Male	33	23	
Female	15	19	
APACHEII	20(10/43)		
SAPS	9.50(3/18)		
SOFA	55.5(18/93)		
WBC	13860(3850/38870)		
ESR	7250(6/143)		
CRP	170.10(7.76/432)		
PCT	3.92(0.61/125.96)		

APACHE II: APACHE II score, SAPS: SAPS score, SOFA: SOFA score, WBC: White blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, PCT: procalcitonin

Among the intensive care unit patients clinically diagnosed with sepsis, blood cultures showed Staphyloccocus hominis in 6 (6.7%), Candida in 3 (3.3%), Klebsiella pneumoniae in 1 (1.1%), Staphyloccocus haemolyticus in 1 (1.1%), and Staphyloccocus haemolyticus in 1 (1.1%). Staphylococcus capitis, Enterococcus faecium growth was detected in 1 patient (1.1%) and Escherichia coli growth was detected in 1 patient (1.1%), and no microorganisms were detected in the blood culture of 32 patients (35.6%).

Table 1. Correlation of variables in patients with sepsis

		Presepsin	Angiopoietin 1	Angiopoietin 2	APACHE II	SAPS	SOFA	WBC	ESR	CRP	PCT	7-day mortality	28-day mortality
Presepsin	**r**	1	0.781	0.711	-0.123	-0.074	-0.167	-0.009	-0.65	-0.092	-0.138	0.102	0.168
	p	-	<0.001	<0.001	0.405	0.616	0.255	0.954	0.659	0.533	0.349	04.89	0.255
Angiopoietin 1	**r**	0.781	1	0.877	-0.187	-0.067	-0.135	0.028	-0.023	-0.080	-0.122	0.095	0.181
	p	<0.001	-	<0.001	0.203	0.651	0.359	0.850	0.875	0.590	0.409	0.523	0.218
Angiopoietin 2	**r**	0.711	0.877	1	-0.199	-0.186	-0.239	-0.132	-0.053	-0.243	-0.300	-0.018	0.144
	p	<0.001	<0.001	-	0.175	0.207	0.102	0.371	0.718	0.097	0.038	0.902	0.329
APACHE II	**r**	-0.123	-0.187	-0.199	1	0.677	0.668	-0.050	0.256	0.059	0.107	-0.015	0.112
	p	0.405	0.203	0.175	-	<0.001	<0.001	0.734	0.080	0.689	0.471	0.918	0.447
SAPS	**r**	-0.074	-0.186	-0.098	0.677	1	0.784	0.015	0.233	-0.054	0.031	-0.098	0.114
	p	0.616	0.207	0.507	<0.001	-	<0.001	0.918	0.111	0.715	0.835	0.507	0.441
SOFA	**r**	-0.167	-0.239	-0.075	0.668	0.784	1	-0.041	0.291	0.047	0.028	-0.075	0.002
	p	0.255	0.102	0.613	<0.001	<0.001	-	0.780	0.044	0.750	0.868	0.613	0.991
WBC	**r**	-0.09	0.028	-0.132	-0.050	0.015	-0.041	1	0.106	-0.097	0.176	-0.005	-0.093
	p	0.954	0.850	0.371	0.734	0.918	0.780	-	0.471	0.514	0.233	0.975	0.529
ESR	**r**	-0.065	0.023	-0.053	0.256	0.233	0.291	0.106	1	0.356	-0.075	-0.180	-0.203
	p	0.659	0.875	0.718	0.080	0.111	0.044	0.471	-	0.013	0.613	0.221	0.166
CRP	**r**	-0.092	-0.80	-0.243	0.059	-0.054	0.047	-0.097	0.356	1	0.524	0.241	-0.125
	p	0.533	0.590	0.097	0.689	0.715	0.750	0.514	0.013	-	<0.001	0.099	0.396
PCT	**r**	-0.138	-0.122	-0.300	0.107	0.031	0.025	0.176	-0.075	0.524	1	0.316	0.059
	p	0.349	0.409	0.038	0.471	0.835	0.868	0.233	0.613	<0.001	-	0.029	0.689
7-day mortality	**r**	0.102	0.095	-0.018	-0.015	-0.098	-0.075	-0.005	-0.180	0.241	0.316	1	0.515
	p	0.489	0.523	0.902	0.918	0.507	0.613	0.975	0.221	0.099	0.029	-	<0.001
28-day mortality	**r**	0.168	0.181	0.144	0.112	0.114	0.002	-0.093	-0.203	-0.125	0.059	0.515	1
	p	0.255	0.218	0.329	0.447	0.441	0.991	0.529	0.166	0.396	0.689	<0.001	-

Table 3. Serum Presepsin, Angiopoietin 1 and Angiopoietin 2 Levels of the patient and control groups

	Patients	Control	p
Presepsin	0.60(0.04/10.77)%95GA0.68-2.12	0.40(0.02/8.17)%95GA0.22-0.99	<0.001
Angiopoetin1	226.86(37.36/4423.75)%95GA313.21-949.29	128.52(5.45/264.44)%95GA105.27-152.30	<0.001
Angiopoetin2	113.57(28.13/1415.67)%95GA155.10-363.19	50.86(1.51/146.20)%95GA40.92-62.07	<0.001

Candida growth was detected in the urine culture of 10 (11.1%) of the intensive care unit patients clinically diagnosed with sepsis, Escherica coli growth was detected in 1 (1.1%), and Alpha hemolytic streptococcus growth was detected in 1 (1.1%), and no urine culture was detected in 36 patients (40%). No microorganisms could be produced.

Among the intensive care unit patients clinically diagnosed with sepsis, 1 (1.1%) had Aspergillus, 1 (1.1%) had Escherica coli, 1 (1.1%) had Klebsiella pneumoniae, 1 (1.1%) had Acinetobacter, 1 (1.1%) had Acinetobacter, and 1 (1.1%) had Aspergillus in their sputum culture. Candida, Pseudomonas aeruginosa growth was detected in 1 patient (1.1%) and Stenotrophomonas maltophilia growth was detected in 1 patient (1.1%), and no microorganisms were detected in the sputum culture of 38 patients (42.2%).

As a result of the evaluation made by ROC analysis, it was seen that serum presepsin value had diagnostic value in diagnosing sepsis (AUC: 0.74, 95%CI: 0.64–0.85, p<0.001). The recommended limit value for this value was determined as 0.47, and 73% sensitivity and 62% specificity were determined (Figure 1).

As a result of the evaluation made by ROC analysis, serum angiopoietin 1 value was found to have diagnostic value in diagnosing sepsis (AUC: 0.80, 95%CI: 0.71–0.89, p<0.001). The recommended limit value for this value was determined as 178.24, and 69% sensitivity and 69% specificity were determined (Figure 2).

As a result of the evaluation made by ROC analysis, serum angiopoietin 2 value was found to have diagnostic value in diagnosing sepsis (AUC: 0.89, 95%CI: 0.82–0.95, p<0.001). The recommended limit value for this value was determined as 77.56, with a sensitivity of 84% and a specificity of 83% was determined (Figure 3).

As a result of the evaluation made by ROC analysis, the success of serum presepsin value in predicting 7-day mortality in patients with sepsis was evaluated (AUC: 0.56, 95%CI: 0.395–0.725, p: 0.484). The cutoff value for this value was determined as 0.59, and 60% sensitivity and 57% specificity were determined. The success of serum angiopoietin 1 value in predicting 7-day mortality in patients with sepsis was evaluated (AUC: 0.54, 95%CI: 0.391–0.720, p: 0.517). The cutoff value for this value was determined as 226.86, and 51% sensitivity and 50% specificity were determined. The success of serum angiopoietin 2 value in predicting 7-day mortality in patients with sepsis was evaluated (AUC: 0.49, 95%CI: 0.316–0.663, p:0.900). The cutoff value for this value was determined as 110.64, and 40% sensitivity and 38% specificity were determined (Figure 4).

As a result of the evaluation made by ROC analysis, the success of serum presepsin value in predicting 28-day mortality in patients with sepsis was evaluated (AUC: 0.61, 95%CI: 0.433–0.785, p: 0.251). The cutoff value for this value was determined as 58.50, and 60% sensitivity and 77% specificity were determined. The success of serum angiopoietin 1 value in predicting 28-day mortality in patients with sepsis was evaluated (AUC: 0.62, 95%CI: 0.441–0.794, p: 0.215). The cutoff value for this value was determined as 209.75, and 69% sensitivity and 62% specificity were determined. The success of serum angiopoietin 2 value in predicting 28-day mortality in patients with sepsis was evaluated (AUC: 0.59, 95%CI: 0.427–0.760, p:0.324). The cutoff value for this value was determined as 110.64, and 55% sensitivity and 54% specificity were determined (Figure 5).

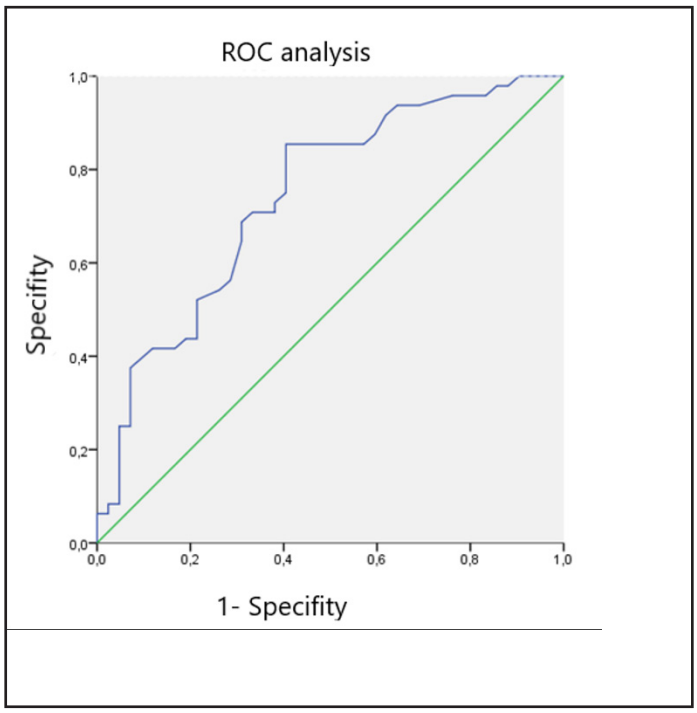

Figure 1. ROC Analysis of Serum Presepsin Level in the Diagnosis of Sepsis

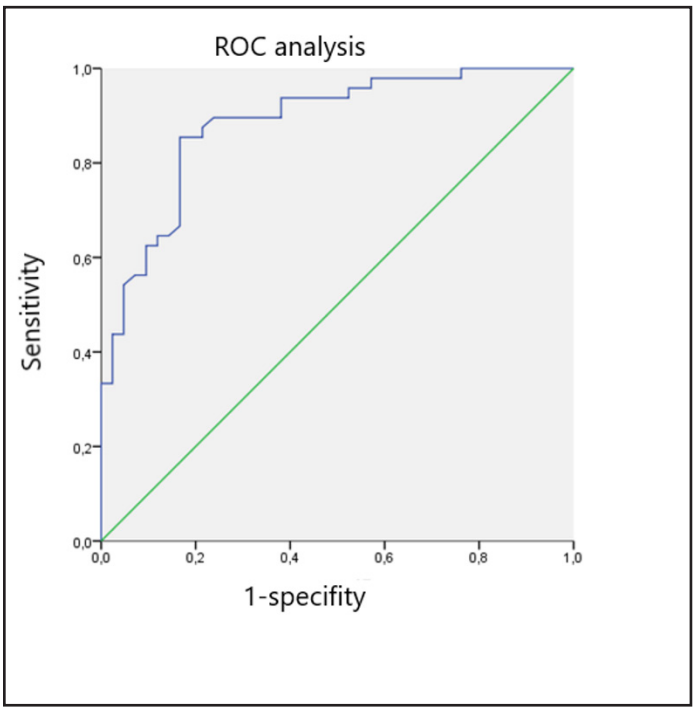

Figure 3. ROC Analysis of Serum Angiopoietin 2 Level in Sepsis Diagnosis

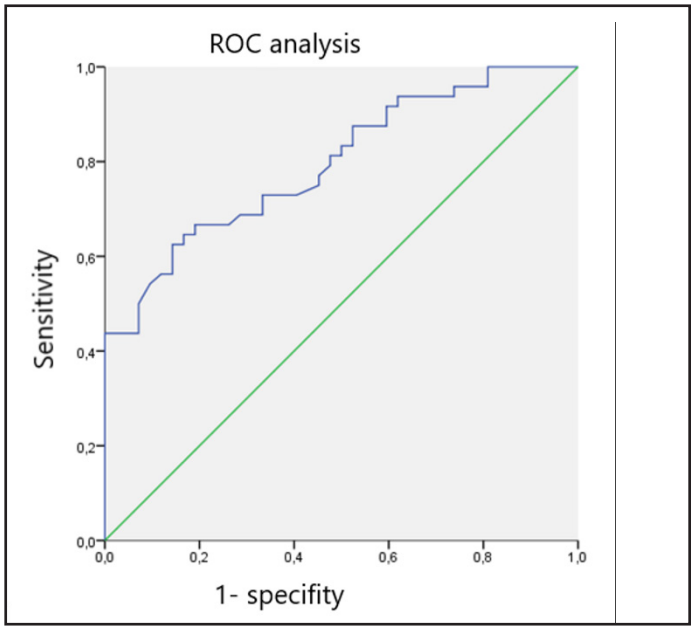

Figure 2. ROC Analysis of Serum Angiopoietin 1 Level in Sepsis Diagnosis

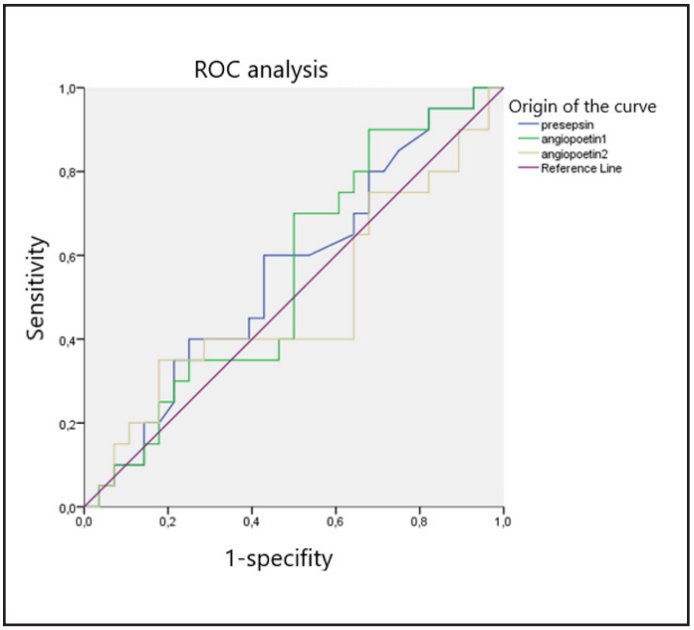

Figure 4. ROC Analysis of Presepsin, Angiopoietin 1, and Angiopoietin 2 in Predicting 7-Day Mortality in Patients with Sepsis

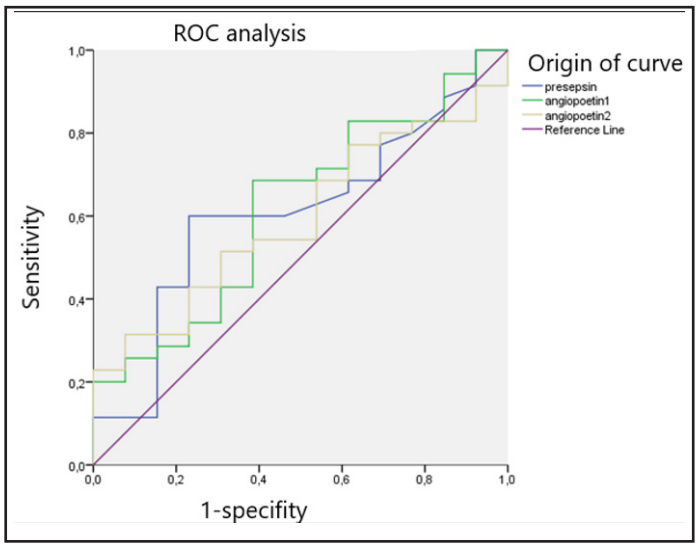

Figure 5. ROC Analysis of Presepsin, Angiopoietin 1, and Angiopoietin 2 in Predicting 28-Day Mortality in Patients with Sepsis

DISCUSSION

Sepsis; It is a syndrome in which various biochemical response abnormalities occur as a result of the host's exaggerated inflammatory response to microorganisms and is a common condition in intensive care units. Although its true incidence is unknown, it is accepted to be one of the main causes of mortality in intensive care units worldwide [5].

In a study conducted by Stoller et al. [6] in which epidemiological data in the United States (USA) were examined, it was found that the incidence of sepsis was increasing every year. In another study by Angus et al., 750,000 sepsis cases were detected annually. The incidence rate per 1000 cases was found to be 5/1000 in patients aged 60-64, while it was 26/1000 in patients older than 85 years of age. The results of this data analysis reveal the fact that overall sepsis cases are progressing faster than expected population growth [3]. That is, the incidence of sepsis varies greatly by age group and increases steadily over the years.

The cost of sepsis and post-sepsis care continues to be a serious health burden on governments all over the world. According to 2013 statistical data in the USA, the cost of sepsis was calculated as 23 billion dollars. With this determined cost amount, sepsis has been accepted as the disease with the highest treatment cost in US hospitals [7]. In 2011, it was estimated that the daily cost of sepsis in the USA was 55 million dollars and the annual cost was approximately 20 billion dollars. This value means a fourfold or 11% increase compared to the cost in 1997 [7].

The cost of sepsis varies depending on the etiological situation, such as whether it develops in or outside the hospital. It was determined that the highest cost was due to hospital-acquired sepsis. While the cost of community-acquired sepsis is thought to be 7000 dollars per patient, the cost of hospital-acquired sepsis is estimated to be 32,000 dollars [8]. This may be caused by microorganisms that are resistant to standard antibiotics.

With the 3rd International Consensus Definition made in 2016, the definitions of sepsis and septic shock were reviewed and the use of the definition of severe sepsis was abandoned. SOFA scoring has come to the fore in the new approach known as Sepsis 3 definitions. The reason for this is attributed to the data in the underlying study. In the relevant study, in-hospital mortality in the non-ICU group was found to be 3-14 times higher in patients with qSOFA>2 than in those with qSOFA<2. In the study, qSOFA, which is a simpler model, was evaluated as a better predictor than SOFA outside the ICU; The working group recommends that the SOFA score be over 2 for the diagnosis of sepsis and that the qSOFA score be used to evaluate the suspicion of sepsis outside the ICU [9].

Early diagnosis and treatment of septic patients at high risk is very important to increase survival associated with sepsis, which continues to be an important public problem. However, since there is no ideal prognostic marker to diagnose sepsis, difficulties are encountered in diagnosing these patients with a high risk of death in the early period. Due to the delay in diagnosis of the disease and the rapid progression that occurs due to the nature of the disease, multiple organ failure and death due to sepsis become inevitable in a short time. It is known that individuals who recover from sepsis also struggle with long-term physical, psychological and cognitive problems [10].

Despite the advances in antibiotics and other supportive treatments for patients with sepsis, unfortunately the incidence of sepsis is gradually increasing and death rates as a result of complications arising from sepsis continue to remain at an undesirably high level [11,12]. Therefore, various clinical scores have been developed to determine the mortality risk of patients at the time of admission and to provide appropriate therapeutic interventions. The most commonly used clinical scores in clinical practice are the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score [13,14]. Recently, negative criticisms about these scorings have accelerated the search for alternative

biomarkers to diagnose sepsis [15].

Dozens of biomarkers have been investigated for use in the diagnosis and follow-up of sepsis. In a study in which more than 3000 articles published in 2010 were scanned, more than 170 biomarkers were evaluated in patients with sepsis. It may be useful in the diagnosis of sepsis.

It was determined that the sensitivity and specificity of only 5 of the 34 parameters evaluated were above 90%. Although these markers are more potential than CRP and PCT, which are used in routine practice, they have not been used routinely due to their difficulty in using them in practice and their high costs. However, obtaining different results in different studies on molecules causes discussions about molecules. Therefore, few parameters are used for this purpose in clinical practice. The most preferred among these are procalcitonin and C-reactive protein [16,17].

In our study, we examined the diagnostic evaluation of presepsin, angiopoietin 1 and angiopoietin 2 in the diagnosis of sepsis, intensive care scoring systems, acute phase reactants (WBC, CRP) between patients diagnosed with sepsis according to Sepsis 3 definitions at the time of admission to the internal medicine intensive care unit and the healthy control group. , ESR and PCT) were evaluated using the data of patients who died and survived in intensive care at the end of the 7th and 28th days to evaluate whether they provide information about the course of sepsis and their power in predicting this course.

In our study, the median age of the control group was 65 (44/85) while the median age of the patient group was calculated as 68 (21/93). While the control group consisted of a total of 42 cases, 23 of whom were males and 19 of whom were females, the patient group consisted of a total of 48 cases, 33 of whom were males and 15 of whom were females. The patient group and the control group were statistically similar in terms of age and gender. 43.8% of the patients with clinically diagnosed sepsis were found in blood cultures taken at the time of admission; Microorganism growth was detected at a rate of 33.33% in urine cultures and 17.07% in sputum cultures. Although the most common infection focus in studies is the lung, the 2nd and 3rd most common infection focus depending on the patient population may be the urinary system or abdomen. Since the majority of our patient population consists of endocrinology, hematology, nephrology and oncology service patients, immunosuppression, which is common in the course of diseases in these departments, explains the frequency of bloodstream infections seen in the patients in our study.

In a study by Shozushima et al. [18], PCT, CRP, IL-6 and presepsin were compared diagnostically. In this study, presepsin level was 294.0 ± 121.4 pg/mL in healthy individuals; 721.0 ± 611.3 pg/mL in those with local infection; 333.5 ± 130.6 pg/mL in patients with SIRS; 817.9 ± 611.3 pg/mL in sepsis patients; and was found to be 1992.9 ± 1509.0 pg/mL in patients with severe sepsis. In this study, presepsin levels were found to be significantly higher in patients with sepsis than in healthy individuals. Diagnostically, when compared to PCT, CRP, IL-6, AUC was found to be highest in the presepsis in the ROC analysis (Presepsin; 0.845, PCT; 0.652, CRP; 0.815; IL-6; 0.672).

In a study conducted by Liu et al. [19], the level of presepsin was examined in a group of 859 patients with SIRS, sepsis and septic shock, and a group of 131 healthy volunteers. In the study, presepsin levels increased in correlation with the severity of sepsis, presepsin AUC was greater than PCT in diagnosing sepsis and predicting septic shock, presepsin AUC was lower than PCT and APACHE II score in predicting 28-day mortality, and patients who died at the end of 28 days had higher presepsin AUC than PCT. They reported that presepsin levels were significantly higher than normal and that presepsin levels were correlated with PCT and APACHE II score.

In a meta-analysis by Kondo et al. [20], the diagnostic value of procalcitonin and presepsin in intensive care unit patients with sepsis was investigated. In the analysis of nineteen observational studies, data from 3012 patients were evaluated. When comparing presepsin with procalcitonin, the AUC for presepsin was found to be 0.84 in the ROC analysis. In addition, the sensitivity of presepsin in the diagnosis of sepsis was determined to be 0.84 and its specificity was 0.73.

In our study, we found that the level of presepsin was higher in patients with sepsis than in the healthy control group and found it to be statistically significant ($p<0.001$). It was found to be highly sensitive and specific for a cuttoff value of 0.47 mg/L in diagnosing sepsis. Presepsin was found to be over 50% sensitive and specific in predicting 7-day and 28-day mortality. A negative correlation was detected between Presepsin and APACHE II, SAPS and SOFA scores, which are examined as intensive care scoring systems, but it was not found to be statistically significant. In addition, a negative correlation was detected between CRP,

PCT and ESR, which were evaluated as acute phase reactants within the scope of the study, and presepsin, but it was not found to be statistically significant. A positive correlation was detected between presepsin and 7- and 28-day mortality, but it was not statistically significant. There was a negative correlation between presepsin and leukocyte count, but the failure to reach statistical significance was attributed to the small number of patients.

Although angiopoietins act as one of the main regulatory molecules of angiogenesis, they also play a role in the inflammation cascade in the body. In particular, angiopoietin 1 is released from pericytes and angiopoietin 2 is released from endothelial cells [21]. Both angiopoietin 1 and angiopoietin 2 bind to the same receptor, the immunoglobulin-like ring epidermal growth factor homologous domain 2 (Tie-2). While angiopoietin 1 increases vascular development and stability, it suppresses inflammation and ensures the survival of endothelial cells. On the contrary, angiopoietin 2 stimulates vascular activation, inflammation, vascular permeability and neoangiogenesis.

In the study conducted by Melendez et al. [22] in 45 pediatric patients diagnosed with sepsis and 49 septic shock, they found the angiopoietin 2/angiopoietin 1 ratio to be above 2 in patients with septic shock. In the same study, the average of angiopoietin 1 was found to be 11,884 pg/mL in patients with sepsis, while the average of angiopoietin 2 was found to be 5659 pg/mL. In the sepsis animal study conducted by König et al. [23] on dogs, the average angiopoietin 2 level in dogs with sepsis was found to be 21.2 ng/mL, while the average angiopoietin 2 level in healthy dogs was found to be 7.6 ng/mL. In the same study, the AUC for angiopoietin 2 in the diagnosis of sepsis was found to be 0.75. In a study conducted by Gutbier et al. [24] consisting of 148 pneumonia patients and 395 healthy volunteers, serum angiopoietin 1 levels were found to be lower in patients with pneumonia compared to healthy subjects, while serum angiopoietin 2 levels were found to be high. In the same study the analysis performed to predict 28-day mortality, the AUC for serum angiopoietin 2 was found to be 0.725. The study by Zonneveld et al. [25] showed that serum angiopoietin 2 levels and angiopoietin 2/angiopoietin 1 ratio were found to be higher in newborn patients with early-onset sepsis, both blood culture positive and negative, compared to healthy newborn babies. However, angiopoietin 1 level was found to be lower.

In our study, it is found that the level of angiopoietin 1 was higher in patients with sepsis than in the healthy control group and found it to be statistically significant ($p<0.001$). Angiopoietin 1 was found to be highly sensitive and specific for the diagnosis of sepsis with a cut-off value of 178.24 pg/mL. It was found to be over 50% sensitive and specific in predicting 7-day and 28-day mortality. A negative correlation was detected between angiopoietin 1 and APACHE II, SAPS and SOFA scores, which are examined as intensive care scoring systems, but it was not found to be statistically significant. Additionally, a negative correlation was detected between CRP, PCT and ESR, which were evaluated as acute phase reactants within the scope of the study, and angiopoietin 1, but it was not found to be statistically significant. A positive correlation was detected between Angiopoietin 1 and 7-day and 28-day mortality, but it was not statistically significant. There was a positive correlation between angiopoietin 1 and leukocyte count, but the failure to reach statistical significance was attributed to the small number of patients.

This study found that angiopoietin 2 levels were higher in patients with sepsis than in the healthy control group and were statistically significant ($p<0.001$). It was found to be highly sensitive and specific for the cutoff value of 77.56 pg/mL in diagnosing sepsis. It was found to be over 50% sensitive and specific in predicting 7-day and 28-day mortality. A negative correlation was detected between Angiopoietin 2 and APACHE II, SAPS and SOFA scores, which are examined as intensive care scoring systems, but it was not found to be statistically significant. Additionally, a negative correlation was detected between CRP, WBC and ESR, which were evaluated as acute phase reactants within the scope of the study, and angiopoietin 2, but it was not statistically significant. Additionally, a negative correlation was detected between serum angiopoietin 2 and procalcitonin and 7-day mortality, but the failure to reach statistical significance was attributed to the small number of patients.

CONCLUSIONS

Diagnostic evaluation of presepsin, angiopoietin 1 and angiopoietin 2 in sepsis, SOFA, SAPS and APACHE II scoring systems, acute phase reactants (WBC, The results of our prospective study, in which we aimed to compare whether CRP, ESR and PCT) provide information about the course of sepsis using 7th and 28th day mortality data and their power in predicting this process, are as follows: Our study was conducted with a patient group consisting of 48 cases, 33 men and 15 women, and a control group consisting of 42 cases, 23 men and 19 women. The median age of the patient group was calculated as 68 (21/93)

and the median age of the control group was calculated as 65 (44/85). No statistically significant difference was determined between the patient and control groups in terms of demographic characteristics. In our study, microorganism growth was detected at a rate of 43.8% in blood cultures, 33.33% in urine cultures and 17.07% in sputum cultures taken at the time of admission of patients clinically diagnosed with sepsis; It was thought that the immunosuppressive state in the patient group may be effective in the high rate of bloodstream infection detection. Presepsin, angiopoietin 1 and angiopoietin 2 levels in the patient group were found to be statistically significantly higher than in the healthy control group, and they were found to be highly sensitive and specific in diagnosis. Presepsin, angiopoietin 1 and angiopoietin 2 levels were found to be successful with high sensitivity and specificity in predicting 7 and 28-day mortality in patients with sepsis.

Conflict of interest: None declared.

Funding: Study was supported by Gaziantep University Scientific Research Projects with project number TF.UT.19.29.

Informed Consent: Written permission was obtained from the patients

Ethical Approval: The Gaziantep University Clinical Researches Ethics Committee authorized the research design (Approval date: 17.04.2019).

Author Contributions: Conception: YH; ANG - Design: ANG - Supervision: YH - Fundings: YH; ANG -Materials: YH - Data Collection and/or Processing: YH; ANG - Analysis and/or Interpretation: YH - Literature: YH; ANG- Review: YH- Writing: YH;ANG- Critical Review: YH.

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How to Cite;

Yildiz H, Acar NG (2024) New Biomarker Candidates of Sepsis: Diagnostic and Prognostic Value of Presepsin, Angiopoietin 1 and 2. Eur J Ther. 30(3):292-302. https://doi.org/10.58600/eurjther2090

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):303-312.
https://doi.org/10.58600/eurjther2143

Original Research

Clinicopathological Features of Elderly Patients with Colonic Volvulus

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Received: 2024-04-14 **Accepted:** 2024-05-07 **Published Online:** 2024-05-08

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ABSTRACT

Objective: Sigmoid volvulus is most commonly seen in patients between 60 and 80 years old. The management of volvulus depends on its location and clinical presentation. The fundamental aspects of treatment include evaluating the viability of the colon, relieving the obstruction, and preventing the possibility of recurrence. We aimed to present geriatric colonic volvulus patients treated in a single center and compare the mortality and morbidity of patients who underwent surgery with or without colonoscopic detorsion.

Methods: Patients diagnosed with colonic volvulus and treated in this hospital were included in the study. Mortality rates of patients who underwent and did not undergo preoperative colonoscopic detorsion were compared statistically. In addition, diseases that affect the quality of life and cause deterioration in bowel movements and habits were determined, and these diseases' effect on mortality was evaluated.

Results: Forty-four patients who underwent emergency surgery due to volvulus were included in our study. There was sigmoid colon perforation in two patients and cecum perforation in 1 patient. Two patients had cecal volvulus, and right hemicolectomy was performed in these patients; anastomosis was performed in one, and ileostomy was performed in the other. Sigmoid resection was performed in 36 patients, subtotal colectomy in 5 patients, right hemicolectomy in 2 patients, and sigmoidopexy with laparotomy and reduction in 1 patient. Thirteen patients (29.5%) underwent preoperative colonoscopy, and in eight cases, the procedure was conducted a day before the surgery, with the operation being carried out semi-urgently the next day.

Conclusion: Intestinal volvulus is a rare condition that can occur in any part of the large intestine. However, it is a severe medical issue that requires prompt diagnosis and treatment due to the possibility of intestinal damage and mortality.

Keywords: Mortality, Sigmoid Colon, Volvulus

INTRODUCTION

Mechanical or non-mechanical factors can cause colon obstruction (CO) in adults. The three most common mechanical causes of CO are obstruction due to colon or rectal cancer, diverticular stricture, and colon volvulus. Colon volvulus is a condition characterized by the colon twisting around its mesentery [1, 2]. The excess segment in the mesentery of the colon causes luminal obstruction in the volvulized segment and proximal to it. This process can cause compromised blood supply to the colon, which can lead to gangrene, ischemia, and even perforation [3-5].

Sigmoid volvulus is a medical condition typically affecting older men in developed countries such as the United States. It is most commonly seen in patients between the ages of 60 and 80 who may have chronic constipation, neuropsychological disorders, or other underlying health issues [3, 4, 6]. Cecal volvulus is a condition that typically occurs in younger patients and is more common in women. The treatment for volvulus is determined by its location and the symptoms it presents. The fundamental aspects of treatment include evaluating the viability of the colon, relieving the obstruction, and preventing the possibility of recurrence. It is important to note that recurrent volvulus without surgical intervention is common, and each subsequent recurrence carries the risk of ischemia and perforation. Therefore, it is crucial to seek medical attention promptly to prevent complications [7-10]. In a study evaluating 48 patients operated on for acute colonic volvulus, extraperitonealization and colon fixation were performed in 11 patients, and it was reported that 1 patient required resection due to recurrence, but this technique is a new method and studies with a high level of evidence have not yet been published in the literature. Although non-resection methods have been tried in volvulus patients, there is currently no more effective method than operations that require resection of the problematic segment [11].

We aimed to present the clinical characteristics of geriatric colonic volvulus patients treated in a single center and compare the mortality and morbidity of patients who underwent surgery with or without colonoscopic detorsion.

Main Points;

- Evaluating the suitability and implementation of colonoscopic detorsion in colonic volvulus patients presenting to the emergency department can reduce hospital mortality.

MATERIALS AND METHODS

This study aims to retrospectively examine geriatric patients who made surgery procedure for colonic volvulus between August 2010 and January 2023 at the General Surgery Clinic of the Haydarpaşa Numune Training and Research Hospital of the University of Health Sciences. The institution's Ethics Committee (Ethics Committee Approval Number: E-62977267-240761645/2024) approved the study protocol. Patients were selected by scanning the hospital database. Patients diagnosed with colonic volvulus and treated in this hospital were included in the study. According to the age categories of the World Health Organization, patients are divided into two groups: old (60 years and above) and young (59 years and below). In this study, the geriatric patient group was taken into consideration. 12 patients defined by WHO as young patients were excluded from the study. Patients with no data records were excluded from the study. Comorbidities, mortality rates, gender, age, surgical procedures performed, preoperative colonoscopic decompression, demographic and clinical characteristics of the patients were examined. Mortality rates of patients who underwent and did not undergo preoperative colonoscopic detorsion were compared statistically. In addition, diseases that affect the quality of life and cause deterioration in bowel movements and habits were determined, and these diseases' effect on mortality was evaluated [4]. All patients underwent nasogastric suction and electrolyte correction and received broad-spectrum antibiotics immediately upon admission for active resuscitation.

Charlson comorbidity Index (CCI) is an evaluation parameter that shows preoperative mortality and 10-year survival in patients with Colonic Volvulus. Preoperative CCI was evaluated statistically in the groups in which patients developed and did not develop mortality. The patient groups were compared by estimating the mortality of the groups with and without preoperative detorsion colonoscopy using CCI [12]. The laboratory parameters of the patients were examined and evaluated and it was reported whether there were any statistical differences between these groups. Values were given using the Clavien Dindo complication classification to evaluate the complications of the patients in the postoperative period [13].

Statistical Analysis

Statistical analyses were performed using IBM SPSS software, version 23.0 (IBM Corporation, Armonk, NY, USA). The average age, gender, and clinical findings of the individuals included in the study were determined by descriptive statistical methods, as well as their frequencies and percentages. It was examined whether the numerical variables showed normal distribution using visual and analytical methods. Comparisons were made using the Student's t-test to compare normally distributed numerical variables and the Mann-Whitney U test for non-normally distributed parameters. The chi-square and Fisher's exact test were used for categorical and nominal variables in pairwise comparisons. In all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Forty-four patients who underwent emergency surgery due to volvulus were included in our study. Demographic data of the patients included in the study are presented in Table 1. 25 (56.8%) of the patients had chronic diseases that could cause constipation or immobilization. Out of the total number of patients examined, 3 (6.8%) had a cerebrovascular accident (CVA), 2 (4.5%) had hypothyroidism, 2 (4.5%) had Parkinson's disease, 5 (11.3%) had Alzheimer's disease, 3 (6.8%) had epilepsy, 2 (4.5%) had Chronic Renal Failure (CRF), 8 (18.8%) had Congestive Heart Failure (CHF), 7 (15.9%) had Chronic Obstructive Pulmonary Disease (COPD), and 12 (27.2%) had diabetes mellitus.

There was sigmoid colon perforation in two patients and cecum perforation in 1 patient. Two patients had cecal volvulus, and right hemicolectomy was performed in these patients; anastomosis was performed in one, and ileostomy was performed in the other. Sigmoid resection was performed in 36 patients, subtotal colectomy in 5 patients, right hemicolectomy in 2 patients, and sigmoidopexy with laparotomy and reduction in 1 patient. A colostomy was performed in 21 (80.7%) patients, and an ileostomy was performed in 5 (19.3%) patients who developed necrosis during the operation and were thought to have an anastomosis leak. The median value of the length of the removed colon is 36 (18-104) cm, the average value of the width of the colon is 17.63±6.7 cm, the average value of the wall thickness of the colon is 0.43±0.21 cm, the average value of the width of the mesocolon is 5.68±2.85.

Table 1. Demographic data

	Mean ±SD/N (%)	Min-Max
Age	77,36±8,16	60-92
Gender		
Male	33 (%75)	
Female	11 (%25)	

SD: Standard Deviation, Min: Minimum value, Max: Maximum Value

Thirteen patients (29.5%) underwent preoperative colonoscopy, and in eight cases, the procedure was conducted a day before the surgery, with the operation being carried out semi-urgently the next day. One of the patients declined the operation after the colonoscopy and left the hospital. However, he returned 33 days later with abdominal pain and was then taken for surgery. Table 2 compares patient age in both groups, the effect of preoperative colonoscopy on mortality, whether the finding of perioperative perforation causes mortality, and the effect of chronic disease on mortality in volvulus patients who are mortal and do not develop mortality. Table 3 statistically presents the perioperative ostomy opening rates of patients who underwent preoperative colonoscopy and the effect of preoperative colonoscopy on the perioperative ostomy opening rate. Preoperative abdominal tomography imaging and operative images are shown in Figure 1-3.

Table 2. Association of age, preoperative colonoscopy, perforation, and chronic disease with mortality

Patients(N=44)	With Hospital Mortality (N=13)	Without Hospital Mortality (N=31)	p
Age(year) (μ±sd)	79,84±7,69	76,32±8,25	0,195*
Chronic Disease			
Yes	8 (%61,5)	17 (%54,8)	**0,682****
No	5 (%38,5)	14 (%45,2)	
Perforation			
Yes	1 (%7,7)	2 (%6,4)	**1*****
No	12 (%92,3)	29 (%93,6)	
Colonoscopy before surgery			
Yes	2 (%15,4)	11 (%35,4)	**0,282*****
No	11 (%84,6)	20 (%64,6)	

Student's t-test* ***Chi-Square Test** *Fisher's exact* testi

Table 3. The relationship between preoperative decompression colonoscopy and ostomy creation

	With Ostomy (N=26)	Without Ostomy (N=18)	p
Colonoscopy Before Surgery			0,071**
Yes	5 (%19,2)	8(%44,4)	
No	21 (%80,8)	10 (%55,6)	

***Chi-Square Test*

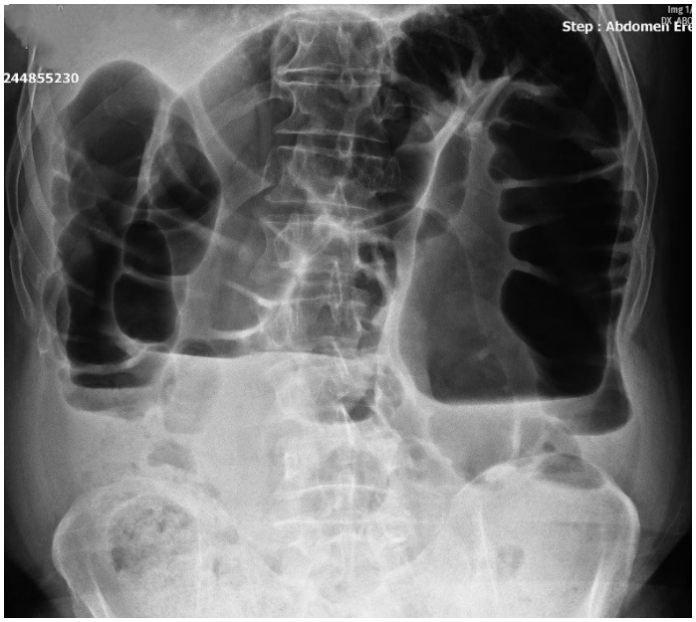

Figure 1. Volvulus Standing Direct Abdominal Radiograph

Figure 2. Volvulus Computerized Tomography Image, a : Coronal section view, b: axial cross-sectional view

Figure 3. Image of Sigmoid Colon in Laparotomy Due to Volvulus

When the American Society of Anesthesiologists (ASA) scores of the patients in our study were examined; 4 (9%) patients were classified as ASA-2, 21 (47.7%) patients were classified as ASA-3, and 19 (43.18%) patients were classified as ASA-4. Mortality was higher in the group with ASA 4. (p=0.002) (Table 4). When patients who developed hospital mortality and those who did not develop hospital mortality were compared, WBC, Hb, neutrophil, plt, CRP, albumin, BUN, creatinine, ALT, AST, pH, lactate, bicarbonate values between the groups. No significant difference was detected between. When the groups with and without colonoscopy were compared, pH and bicarbonate values were statistically significantly higher in the group with preoperative colonoscopy (pH 7.4 vs. 7.36 p=0.021, bicarbonate 24.5 vs. 22.41 p=0.003). No significant difference between these two groups was detected in other laboratory parameters (WBC, Hb, neutrophil, plt, CRP, albumin, BUN, creatinine, ALT, AST, lactate) (Table 5).

When the CCI of the cases was calculated, the average CCI value was found to be 4.74±1.44. The CCI value in the group with hospital mortality was significantly higher than in the

group without mortality (5.46 vs 4.43 p=0.031). There was no significant difference between the CCI values of the groups with and without preoperative colonoscopy (4.62 vs 4.8 p=0.706). CCI, 10-year life expectancy percentage, significantly differed between groups with and without mortality (17.2 months vs 36.3 months p=0.045). When the cases were examined according to the Clavien-Dindo complication classification, Clavien-Dindo III complications developed in 1 (2.3%) patient, Clavien-Dindo IV complications developed in 11 (25%) patients, and Clavien-Dindo V complications developed in 13 (29.5%) patients. In patients with no mortality during follow-up, there was no significant difference in the length of hospital stay between the groups with and without preoperative colonoscopy (p=0.073).

When patients without mortality were followed, the average follow-up period was 46.4 ± 34.7 months. Survival times were significantly different in the groups with and without preoperative colonoscopy (45.5 months vs 25.1 months p=0.045). During follow-up, mortality occurred in 3 (37.5%) patients in the group in which preoperative colonoscopy was performed and in 15 (68.2%) patients in the group in which colonoscopy was not performed, and no statistically significant difference was detected between the two groups (p = 0.21).

Table 4. The effect of preoperative patients' ASA scoring values on mortality

	ASA-2 (N=3)	ASA-3 (N=21)	ASA-4 (N=19)	p
Hospital mortality				0,002*
No	4 (%100)	19 (%90,5)	8 (%42,1)	
Yes	0 (%0)	2 (%9,5)	11 (%57,9)	

ASA: American Society of Anesthesiologists , * *Chi-square test*

Table 5. Laboratory parameters of the patients

	Mean ±SD/N (%)	Min-Max	Preoperative Colonoscopy		P Value	Mortality		P Value
			Yes	No		Yes	No	
WBC (10*3µl)	9,65±6,63	1,6-44,65	7,95±2,36	10,42±7,75	0,389	8,81±5,07	9,99±7,21	0,731
Hb (g/dl)	12,81±3,85	7,5-31,3	12,24±1,77	13,06±4,49	0,727	12,87±6,64	12,79±2,06	0,356
Neutrophil (10*3µl)	7,86±6,34	1,2-41,18	6,05±2,29	8,67±7,38	0,305	7,59±4,79	7,97±6,93	0,989
Plt (10*3µl)	228,83±87,31	49-434	207,76±100,87	238,27±80,64	0,301	215,16±81,12	234,3±90,41	0,528
CRP (mg/dl)	3,66±5,06	0-24,7	1,94±2,46	4,43±5,74	0,068	4,03±3,85	3,51±5,53	0,371
Albumin (g/dl)	4,31±6,24	2,1-43,6	3,64±0,61	4,62±7,53	0,167	3,13±0,66	4,79±7,36	0,117
BUN (mg/dl)	25,11±19,86	0-90,3	23,71±13,34	25,73±22,36	0,936	29,43±24,44	23,38±17,9	0,611
Creatinine (mg/dl)	1,11±0,59	0,39-3,18	0,97±0,34	1,18±0,67	0,648	1,23±0,85	1,07±0,46	0,731
ALT (U/L)	22,85±19,1	5-118	21,38±11,72	23,51±21,77	0,936	30,16±29,16	19,93±12,74	0,208
AST (U/L)	30,07±25,49	11-146	23,38±6,7	33,06±30,04	0,851	40,16±37,57	26,03±18,01	0,117
pH (mmol/l)	7,37±0,04	7,29-7,51	7,4±0,04	7,36±0,04	0,021	7,39±0,06	7,37±0,04	0,293
Lactate (mmol/)	2,02±1,75	0,4-9,2	1,38±0,81	2,3±1,98	0,06	2,6±2,35	1,78±1,43	0,229
Bicarbonate (mmol/l)	23,05±2,85	17,8-33	24,5±2,65	22,41±2,74	0,003	24,16±4,35	22,61±1,91	0,466

WBC: White Blood Cell, Hb: Hemoglobin, PLT: Platelet, CRP: C-reactive protein, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, pH: acid–base balance, * Chi-square test

DISCUSSION

The rate of gangrene in sigmoid volvulus patients ranges from 6.1% to 30.2%, with the highest percentage being 28.2% in the most extensive published series [14]. For patients under 60 years of age, it is recommended to perform mini-laparotomy for sigmoid resection under local anesthesia to reduce mortality and protect the patient from the harmful effects of general anesthesia [15]. A study comparing patients with sigmoid volvulus under 59 and those under 60 showed that mortality and comorbidity were higher in patients under 60 [4, 16]. However, in our study, no significant age difference was found between the groups with and without mortality.

Apart from surgical treatments for colon volvulus, colonic decompression methods are not widely used as the only treatment measure, and methods usually followed by post-decompression surgery are more commonly applied in the clinic. Contrast enema has historically been used for diagnostic and therapeutic reasons in treating colon volvulus [17, 18]. Although there were rare cases described, they were elderly patients with multiple comorbidities and were not suitable for surgery, although they were not fully specified. While the success rate of colonic decompression in sigmoid volvulus is 70-90%, it is generally unsuccessful in cecal volvulus [8, 10, 18-20]. In a study by Ebrahimian et al., sigmoid volvulus decompression colonoscopy had a failure rate of 10.1% [18]. The time interval to non-emergent resection was three days. In addition, it is considered a temporary measure that allows elective or semi-elective surgery after stabilization of the underlying fluid and electrolyte disturbance caused by the disease [6]. It is not considered a definitive treatment method due to the high torsion recurrence (20%-70%) [8, 9, 16]. In our study, preoperative decompression colonoscopy was performed in 13 patients, and the mortality rate in these patients was 15.4%, and the ostomy opening rate was 38.4%. In our study, the highest waiting time after colonoscopy was 33 days for surgery.

Surgical treatment of colonic volvulus can be generally divided into procedures such as resecting the torsioned segment and fixation of the torsioned segment. In previously published series, it has been reported that decompression with fixation or operative detorsion without fixation was used in young patients who developed colon volvulus. This can be explained by the fact that young patients refuse the resective procedure, the surgeon does not want resection in the young patient, or, in some cases, the patient's general condition does not allow colon resection [21, 22]. In Halabi et al.'s study, only 17% of patients received decompression colonoscopy without additional procedures. [4] In a different research, colon resection with restoration of bowel continuity emerged as a superior surgical option, according with a 44% recurrence rate after detorsion alone, a 30% recurrence rate after detorsion with colopexy, and a 13% mortality rate after sigmoidostomy. For uncomplicated sigmoid volvulus, a 9% recurrence and 10% mortality rates were found after colon resection [23]. In our study, reduction and sigmoidopexy were performed in one patient, and no recurrence occurred. We thought that the difficulty of complications that may occur in case of recurrence in the patient group and the delays in hospital admission might be why we did not prefer to wait for post-reduction surgery.

Mortality rates of different surgical procedures are consistent with previously reported data and current studies [4, 24, 25]. There was no significant change in mortality rates compared to old data. It was noted that the mortality rates were lower for patients who were treated with laparoscopy. However, laparoscopy is typically used for patients who have lower comorbidity scores, and these procedures are performed semi-electively after decompression with endoscopy [26, 27]. The effect of semi-elective surgery after decompression with endoscopy to protect against mortality has not been addressed, contrary to previously published data [28, 29]. This effect may be masked by other factors that have a higher impact on mortality. It has been found that delaying surgery after successful colonoscopic decompression to correct the underlying fluid and electrolyte imbalance can reduce mortality rates [4]. The impact of fluid and electrolyte imbalance on mortality rates has not been considered in great detail. A recent study found similar rates of mortality, anastomotic leakage, bleeding, surgical site infection, and wound dehiscence between primary anastomosis and the Hartmann procedure [30]. The most current ASCRS guidelines recommend primary anastomosis in elective cases unless the patient's risk factors conflict with this [31]. The mortality rate varies between 1% and 9% for the colon with intact blood supply and structure and 25% for gangrenous volvulus [4, 17, 18, 22, 32]. Colonic resection in cases of nongangrenous sigmoid volvulus has an acceptably low complication rate when performed as a semi-elective procedure after endoscopic detorsion has been performed as the initial procedure [4, 18, 33]. In their study, Halabi et al., found the mortality rate to be 6.4% in patients who underwent decompression colonoscopy. Our study examines the geriatric population and shows a population with a long time until symptoms appear. Due to this delay in

application, decompression colonoscopy could not be performed on all patients and could only be performed on 13 patients. In our study, mortality was found in 2 patients who underwent decompression (15.3% in the colonoscopy group and 4.5% in the entire patient group). While not statistically significant, patients who underwent colonoscopy had lower rates of ostomy and mortality. The fact that the CCI values of these two compared groups are statistically the same in our study indicates that the groups are similar in terms of mortality risks. We believe this may be because patients who can undergo colonoscopy are typically assumed not to have gangrenous or necrotic colon and are treated accordingly, resulting in lower mortality rates. Our study's high pH and bicarbonate values suggest that this idea is confirmed.

In a study conducted, all colon obstructions admitted to the emergency department between 2002 and 2010 were examined, and it was found that 1.9% of these obstructions were due to volvulus. In the same study, heart failure was found in 16.8% of the patients, Chronic pulmonary disease in 16.8%, kidney failure in 5.8%, and Neurological disorder or paralysis in 31.3%. In their study by Ebrahimian et al., it was reported that 13.7% of those with sigmoid volvulus had signs of Congestive heart failure, 16.5% had Chronic pulmonary disease, and 10.6% had chronic renal failure [18]. Again, the same study reported that patients with frailty had high mortality and morbidity. In our study, CVO in 3 (6.8%) patients, Parkinson's disease in 2 (4.5%) patients, Alzheimer's disease in 5 (11.3%) patients, epilepsy in 3 (6.8%) patients, CRY in 2 (4.5%) patients. CCY was present in 8 (18.8%) patients, and COPD was in 7 (15.9%) patients. When the literature is examined, it is not seen that all constipation etiologies have been questioned in a single study.

Deresse et al. reported that a high ASA score caused adverse perioperative outcomes [34]. Valzdezate et al. reported that postoperative complications and mortality increased in patients with an ASA score of 3 and above [35]. The same study reported that the mortal disease group developed in ASA 4 patients who underwent emergency surgery. Our study's mortality was statistically higher in the ASA 4 patient group.

In the literature, mortality and morbidity are high in volvulus patient groups with CCI >1 [36]. Additionally, intervention with endoscopic methods has been recommended for these patient groups. In the patient group with acute cholecystitis, which is another risky surgery requirement and CCI determines the risk of preoperative mortality, complications were more common in those with CCI>6 [37]. Satheakeerthy et al. found the median CCI score to be 4 in their study [38]. In the same study, they followed up 48% of the patients non-operatively and reported that recurrence developed in 63%. The same study reported that although non-operative follow-up reduced mortality in patients with high CCI, mortality remained high. In our research, CCI was found to be statistically high in the group with hospital mortality.

Limitations

Our study is retrospective and has its limitations. Since it is not possible to determine how long the etiology of chronic constipation has persisted in patients, it is not clear whether there is chronic exposure to these diseases or their early consequences. Some of these weaknesses can be eliminated with a well-designed prospective study, but it will take a long time to reach sufficient patients. The surgical urgency of the disease means that it would be difficult to conduct a randomized trial. Another limitation of our study is that the mechanisms involved in the decisions taken for operations and other procedures by evaluating patients under emergency conditions cannot be fully evaluated.

CONCLUSION

Intestinal volvulus is a rare condition in any part of the large intestine. However, it is a severe medical issue that requires prompt diagnosis and treatment due to the possibility of intestinal damage and mortality. Mortality can be reduced with preoperative decompression in volvulus patients. In addition, it should be aimed to reduce morbidity and mortality with non-surgical methods in patients with comorbid diseases.

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

Informed Consent: All informed consents were taken from all patients.

Funding: None.

Ethical Approval: Ethical approval was obtained (E-62977267-240761645/2024).

Author Contributions: Conception: G, MO; A,C - Design: G,MO;OA,S - Supervision: G,MO;S,O - Fundings: OA,S;S,O

-Materials: S,A;A,EB- Data Collection and/or Processing: Ç,K;A,C - Analysis and/or Interpretation: G,MO;S,A- Literature: Ç,K;G,MO - Review: G,MO; Ç,K - Writing: G,MO;A,C- Critical Review: G,MO;OA,S

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How to Cite;

Gül MO, Aşlayan SO, Çorbacı K, Selman A, Akçay EB, Sunamak O, Akyüz C (2024) Clinicopathological Features of Elderly Patients with Colonic Volvulus. Eur J Ther. 30(3):303-312. https://doi.org/10.58600/eurjther2143

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):313-321.
https://doi.org/10.58600/eurjther1910

Original Research

Comparison of the Post Treatment Outcomes of a Conservative Physiotherapy Protocol for Subacromial Impingement Syndrome in Terms of Acromion Morphology

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Received: 2023-10-31 **Accepted:** 2024-02-06 **Published Online:** 2024-02-09

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ABSTRACT

Objective: The present study aimed to compare the results of a conservative physiotherapy (CP) protocol for subacromial impingement syndrome (SIS) in terms of the morphological types of acromion.

Methods: Fifty patients participated in the present study, and they were divided into 3 groups according to the acromion morphology types. A 8-week CP (4-week treatment period at the clinic and, in addition, an exercise program at home for 4 weeks) was applied to all patients. The patients were evaluated in terms of pain (at rest and activity) by the Visual Analog Scale, range of motion (ROM), joint position sense (laser pointer), muscle strength (digital dinamometer), and functionality (the Shoulder Pain and Disability Index, SPADI) before and after the treatment.

Result: In the pre- and post-treatment changes (delta), the shoulder flexion angle increased less in the type 3 group than in the type 1 and type 2 groups ($p<0.05$). In the shoulder abduction angle, there was a similar increase in the type 3 group compared to the type 2 group, while there was less increase in the type 1 group ($p<0.05$). It was determined that there was more deviation in the change value of shoulder abduction position sense in the type 3 group compared to the other groups ($p<0.05$). There was no difference between the groups in the change values of pain, muscle strength, or the SPADI score ($p > 0.05$).

Conclusion: Type 3 acromion may have a handicap in improving shoulder flexion and abduction ROM and shoulder abduction position compared to other types.

Keywords: Subacromial Impingement Syndrome, Shoulder pain, Acromion, Physiotherapy

INTRODUCTION

Subacromial impingement syndrome (SIS) affects a wide range of populations with various symptoms and pathologies. The most frequent symptoms are pain, weakness, and loss of motion caused by catching muscle tendons in the shoulder [1]. Also, proprioceptive deficits could occur in the shoulder joint after shoulder pathologies and injuries, because of the damage to the capsule, ligaments, glenoid labrum, or pericapsular muscles [2, 3]. Many researchers claim that the morphological type of the acromion is related to SIS. The coracoacromial ligament,

coracoid process and the acromion all form the coracoacromial arch which is the superior border of the subacromial space (SS). Structures around the shoulder like the tendons of rotator cuff muscles, the long head of the biceps brachii muscle tendon and the bursa traverse through the SS. Some studies stated that the hook-shaped acromion could be related to a higher prevalence of SIS, whereas not all researchers have determined this [4-7]. Even if this knowledge does not explain all of the anatomical handicaps that cause impingement syndrome, the structures that pass through the SS in different congestions depending on the type of acromion, may change the probability of pathologies related to this region.

The effect of acromion morphology on the healing processes of pathologies related to the shoulder joint has aroused curiosity. Therefore, some researchers have examined the relationship between the healing outcomes of different types of treatment methods and acromion morphology. However, studies correlating acromion morphology with healing outcomes after conservative physiotherapy methods in SIS are rare [8-10].

Conservative physiotherapy methods on SIS are aimed at achieving pain relief, increasing muscle strength, gaining joint range of motion and sense of joint position, and increasing functionality [8]. Conservative treatment methods include prevention by ergonomics in daily life, resting methods for the joint by orthosis, medical treatment, steroid injections to the SS, and various conventional treatment methods of physiotherapy such as electrotherapy, manual therapy techniques, and exercises [11].

To the best of our knowledge, there is no study comparing the effectiveness of a conservative treatment protocol according to acromion types. The aim of this study is to investigate the effectiveness of conservative treatment on pain, range of motion, joint position feeling, muscle strength, and shoulder disability level in acromion types. In the current study, we examined whether the results of an applied conservative physiotherapy protocol on patients with SIS would make a difference in the healing of pain, range of motion, muscle strength, position sense, and functionality according to the acromion types of patients and assessed the predictive value of acromial morphology in the treatment outcome of patients.

Main Points:

- The pain levels at rest were higher in type III acromion before the treatment than in other acromion types
- In all acromion types, the healing of pain at rest and pain during activity was similar.
- Type III acromion type may create a handicap in the healing process compared to other acromion types.

MATERIALS AND METHODS

Study Design and Participants

The research related to human use has complied with all the relevant national regulations and institutional policies and has followed the tenets of the Declaration of Helsinki. All patients had been informed about the treatment procedure and patient consent had been received.

This prospective study was conducted between October 2019 and April 2020. Patients who were diagnosed with SIS by the physician with magnetic resonance imaging (MRI) and clinical diagnostic tests, who had not received any treatment from the shoulder joint before, and who were undergoing physiotherapy treatment for the first time were included in this study. Patients with a history of upper extremity surgical operations or fractures of the upper extremities, those with acute cervical disc herniation or a neuromuscular disease, who were receiving medical therapy for pain relief, and who attended the treatment sessions less than 80% were excluded.

Fifty-two patients diagnosed with SIS were evaluated in the present study. Two patients did not accept the study. Total of fifty Patients were divided into 3 groups according to the stated acromion morphology types. The acromion types of the patients were determined on the shoulder MR images by a radiologist (Figure 1). During the acromion morphology assessment, Bibliani's method was used to define the types. According to this classification, Type I represented a flat shape (n=16), type II a curved (n=20), and type III a hooked (n=14) undersurface of the acromion [12, 13]. The approval of the Human Research Ethics Committee of Hasan Kalyoncu University with the registration number 2019/100 (Date: 01.10.2019). The study permission was taken from Harran University Research and Application Hospital (No: 66063783-622.99).

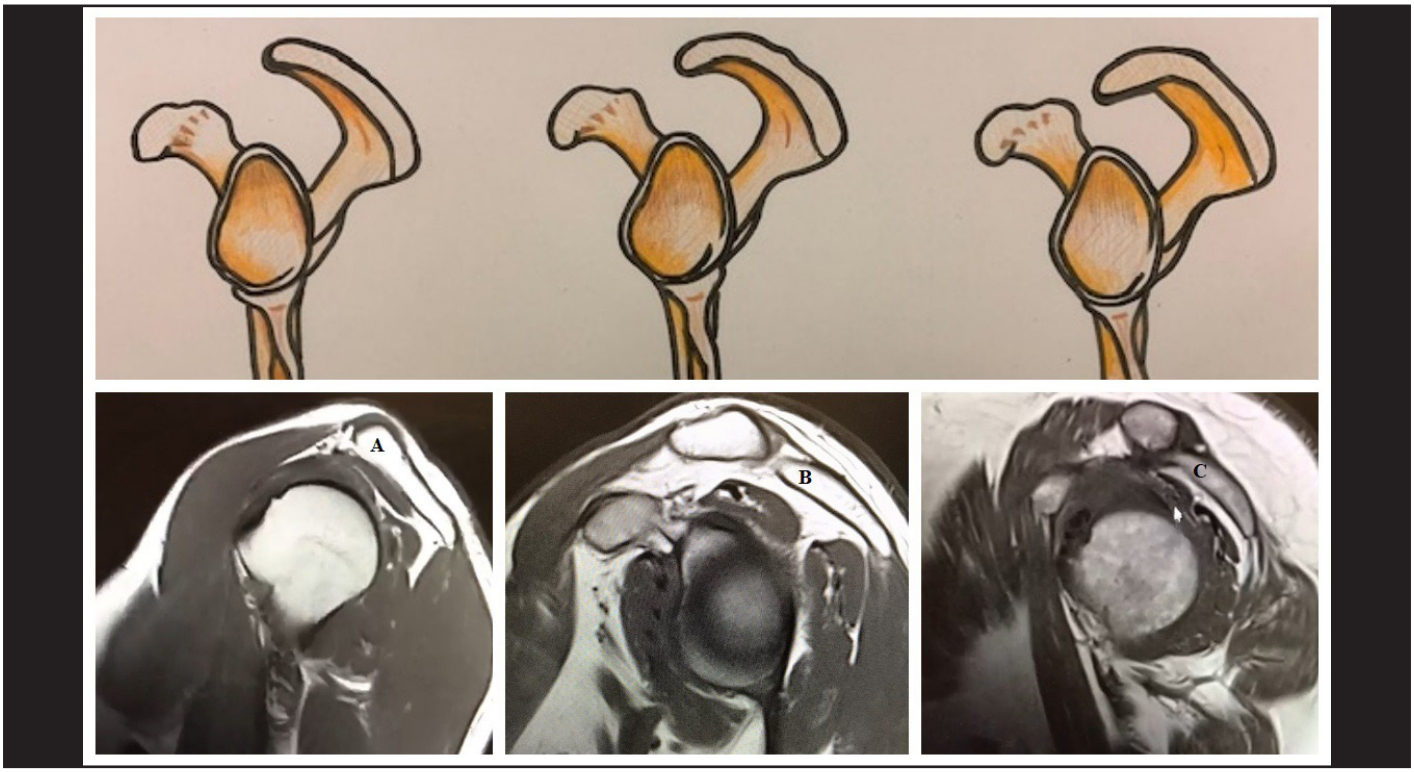

Figure 1. Acromion types, A: Flat shape (Type I), B: Curved shape (Type II), C: Hooked shape (Type III)

Treatment Protocol

Five minutes of ultrasound application (Business Line US 50, Medical Italia, Italy) at a frequency of 1 MHz and intensity of 1.5 watts/cm², conventional TENS (frequency 60-120 Hz, BTL-5000, U) for 20 minutes, Codman's exercises, wheel activities for shoulder, isometric exercises and range of motion exercises, shoulder joint capsule stretching, stabilization exercises for scapular region, and muscle strengthening exercises (shoulder flexor, abductor, extensors, internal and external rotator muscles were strengthened with dumble and therabands in 2 sets of 15 repetitions) were the contents of the treatment protocol for chronic patients. A cold pack was applied to the shoulder region for 10 minutes after the treatment. All modalities of the treatment protocol were applied for 5 days per week and a total of 20 sessions. After a 4-week treatment period at the clinic, the patients were followed up by an exercise program at home for 4 weeks. The exercises performed in the clinic were also given as part of a home program. All the patients were followed up by daily phone calls.

Assessments Methods

The study was blinded, and the evaluators did not know which group the patients were in. The shoulder pain at rest and pain during activities were recorded. A Visual Analog Scale (VAS) was used to determine the pain levels (0-10; 0 means no pain, 10 means the worst pain) [14]. A universal goniometer was used to determine the joint range of motion (ROM). Muscle strength tests for shoulder movements were done by a dynamometer (NK-500, AIPU, Anhui, China) [15]. The joint position sense was evaluated by a laser pointer. During the joint position sense measurements ninety degrees shoulder joint flexion and abduction movements were evaluated. The laser pointer was fixed at 5 cm above the elbow joint with velcro. Then the patient was asked to bring the shoulder joint to ninety degrees of flexion while the patient's eyes were open and the range was measured with a goniometer. The patient held this position for 10 seconds. The projection of the laser pointer on millimeter paper was marked. The patient repeated the movement three times with her eyes open and by imagining the movement. After returning to the neutral position, the patient closed their eyes and repeated the flexion movement three times. The projection of the laser on millimeter paper was marked to state the deviations. The same procedure was performed to measure the joint sense level of shoulder abduction. The starting point was accepted as the origin and during the repetition of motion, the projections of the points on the x and y axes were noted. The deviation between the measurements was calculated [16]. The Shoulder Pain and Disability Index (SPADI) was used to evaluate the level of disability of the participants by

questioning the level of limitation experienced by the participants during personal transportation, care and dressing activities and to measure their current shoulder pain and disability status. The Turkish validity of the scale was conducted by Bumin et al in 2008. The whole scale consists of two subtitles (5 questions for pain sense and 8 questions for disability). These subscales are calculated between 0-100 points (0=no pain, 100=worst imaginable pain) [17].

Statistical Analysis

The SPSS Package Program was used for the statistical analyses (SPSS 23.0 for Windows, Chicago, IL, USA). The normality distribution of the data was analyzed with the Shapiro-Wilk test. In the presentation of non-parametric data, percentage (Q1:25%, Q3:75%), median was used. The Wilcoxon test was used to compare within-group changes of non-parametric data before and after treatment. The comparison of the differences between the groups before and after treatment was analyzed by the Kruskal-Wallis test. A value of P <0.05 was considered statistically significant. A post hoc power analysis was performed to determine whether there was a significant difference between the groups in terms of rest pain according to acromion type. The effect size (f = 0.537) and power (1-β err probe) of the study conducted with a total of 50 subjects were calculated as 0.919. Post-power analysis was performed with G*Power 3.1.9.4 (Franz Faul, Universität Kiel, Germany) [18].

RESULTS

Demographic characteristics of the individuals according to acromion types are given in Table 1. It was stated that 32 % (n=16) of patients had type I, 40 % (n=20) of patients had type II, and 28 % (n=14) of patients had type III acromion.

Intra- and inter-group comparisons of the pre-treatment, post-treatment, and delta (pre-post treatment difference value) values of the groups according to acromion types are shown in Table 2. All groups showed significant improvement in pain scores, joint motion angles, joint position sense, muscle strength, and shoulder disability level before and after treatment (P < 0.001, Table 2). There was a significant difference in the delta values of flexion and abduction joint angles between the groups (P = 0.001, P = 0.040, respectively). Type 1 acromion and type 2 acromion groups had higher delta values of flexion joint angle than the type 3 group (P = 0.002, P = 0.003, respectively, table 3). In the delta value of the abduction joint angle, a significant difference was found only between the type 1 group and the type 3 group (P = 0.049, Table 3). A significant difference was found in the delta of abduction joint position sense between the groups (P = 0.012, Table 3). The abduction joint position sense delta value was lower in the type 3 group than in the type 1 and type 2 groups (P = 0.026, P = 0.024, respectively, table 3).

Table 1. Demographic features of the patients.

	Acromion Type 1 Group (n=16)	**Acromion Type 2 Group (n=20)**	**Acromion Type 3 Group (n=14)**	
	Median (Q1-Q3)	**Median (Q1-Q3)**	**Median (Q1-Q3)**	***P***
Age (year)	55.5 (45-61.75)	55.5 (43.25-64)	50.5 (44.5-61.5)	0.709
BMI (kg/m^2)	29.39 (27.8-30.79)	28.09 (26.35-30.74)	29.31 (27.99-30.22)	0.459
	n	**n**	**n**	
Sex (female/male)	9/7	13/7	8/6	
Affected Side (right/left)	13/3	15/5	11/3	
Dominant side (righ/left)	16	17/3	13/1	

BMI: Body masss index, *P:* Kruskall Wallis test

Table 2. Intragroup comparison according to acromion types

	Acromion type 1 (n=16)			Acromion type 2 (n=20)			Acromion type 3 (n=14)		
	Before	After		Before	After		Before	After	
	Median (Q1-Q3)	Median (Q1-Q3)	*P*	Median (Q1-Q3)	Median (Q1-Q3)	*P*	Median (Q1-Q3)	Median (Q1-Q3)	*P*
PR (cm)	6 (6-7)	4 (3.25-4.75)	*	5 (5-6)	3 (3-4)	*	6 (6-6.25)	4 (3.75-4)	*
PDA (cm)	7.5 (6.25-8)	5 (4-6)	*	7 (7-7.75)	4.5 (3-5)	*	7 (6-8)	5 (4-5.25)	*
Flexion (o)	164 (152-169.25)	175 (166-176)	*	166 (155-171)	175 (170-177)	*	160 (150-163)	163 (156-165)	*
Extension (o)	40 (27-40)	42 (40-44.5)	*	40 (38-40.75)	42 (40-45)	*	40 (37-40.25)	40.5 (40-42)	*
Abduction (o)	158 (145-168)	169 (164-174.75)	*	165 (156-166)	174 (166-175)	*	159 (150-166)	164 (156-171)	*
Adduction (o)	40 (36.5-42)	42.5 (40-45)	*	42 (36-44.25)	45 (42-45)	*	39 (35-42)	44 (40-45)	*
Internal rotation (o)	76.5 (53-84.25)	85 (75-85)	*	76 (65-80)	84.5 (80-85)	*	76.5 (70-82)	83.5 (75-86.25)	*
External rotation (o)	80 (70-84.5)	85 (80-86)	*	76.5 (72-82)	85 (80-87)	*	80 (67.25-83)	85 (78-90)	*
JPSF (cm)	11 (10-12)	8.9 (7.6-10.5)	*	10.9 (9.9-12.5)	8.8 (7-10.1)	*	11.3 (9.6-13)	8.9 (6.7-9.8)	*
JPSA (cm)	11.3 (8.4-12.1)	8 (6.8-9.6)	*	11.9 (9.7-13)	8.5 (7.8-10.2)	*	12.4 (8.7-12.8)	11.5 (8.3-12.1)	*
SF (kg)	6.1 (4.7-7.1)	7.1 (5.5-8.5)	*	6.3 (5.1-7.9)	8.1 (5.5-9)	*	6.8 (5.2-7.5)	7.8 (6.7-8.6)	*
SE (kg)	4.75 (3.6-5.1)	5.1 (4.5-5.5)	*	4.3 (4.1-4.5)	5 (4.5-5.9)	*	4.5 (4.2-5.3)	5.2 (4.5-6.1)	*
SAB (kg)	5.8 (5-7.9)	7 (6-8.5)	*	6.3 (5.2-7.4)	7.5 (6.6-9.3)	*	6.9 (5.25-8.3)	8.1 (6.7-9.3)	*
SAD (kg)	4.1 (3.3-4.8)	4.8 (4.5-5.5)	*	4.4 (4.1-5)	5.1 (4.5-6.4)	*	4.4 (3.9-4.6)	5 (4.5-5.5)	*
SIR (kg)	4.3 (4-4.8)	5 (4.5-5.25)	*	4.3 (3.3-5)	5.2 (4.5-5.7)	*	4.3 (4.2-5)	5 (4.4-6)	*
SER (kg)	4.5 (4.1-5)	5 (4.6-5.5)	*	4.4 (4-5.3)	5 (4.5-5.8)	*	4.4 (4.1-5)	5 (5-5.8)	*
SPADI in pain (score)	67 (63-76)	61 (56-65.5)	*	72 (66-76)	60 (55-66)	*	73 (66-80)	65 (58-70)	*
SPADI functional (score)	63.7 (58.7-69.6)	56.2 (50-61.8)	*	65.6 (61-70)	57.5 (51-62.5)	*	61.8 (60-71)	58 (53.4-63.3)	*
SPADI total (score)	65.7 (61-72)	58.4 (53-62)	*	67 (63-73)	57.6 (53.4-63)	*	66 (62.8-76)	60 (56-65.7)	*

PR: pain at rest, PDA: pain during activity, JPSF: JPS in flexion, JPSA: JPS in abduction, SF: strength of flexion, SE: strength of extension, SAB: strength of abduction, SAD: strength of adduction, SIR: strength of internal rotation, SER: strength of external rotation, JPS: Joint position sense, SPADI: Shoulder Pain and Disability Index * $p<0.001$; Wilcoxon paired two sample test

Table 3. Comparison of delta values between groups

	Acromion type 1 (n=16)	Acromion type 2 (n=20)	Acromion type 3 (n=14)	
	Delta (Δ)	Delta (Δ)	Delta (Δ)	
	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	*P*
PR (cm)	-2 (2-2.75)	-2 (1-2)	-2 (1-2.25)	0.526
PDA (cm)	-2 (2-3)	-2 (2-4)	-2 (1.75-3)	0.527
Flexion (o)	9.5 (14.25-7.25)	8 (14.25-6.25)	4.5 (5.5-1)	0.001#
Extension (o)	2.5 (5-2.5)	2 (5-2)	2 (3-0.75)	0.541
Abduction (o)	9 (19-5.25)	9 (13-5.25)	5 (7.5-4)	0.040#
Adduction (o)	3 (5-0)	3 (5-0)	3 (5-1)	0.982
Internal rotation (o)	7.5 (14-3)	6.5 (12.75-5)	6 (8.25-5)	0.933
External rotation (o)	5 (10-3)	6.5 (10-3)	6 (10.5-5)	0.628
JPSF (cm)	-1.7 (0.9-3.6)	-2.6 (1-3.7)	-2.2 (0.6-3.2)	0.655
JPSA (cm)	-1.7 (1.1-3.5)	-2.1 (0.9-3.5)	-0.9 (0.5-1.2)	0.012#
SF (kg)	1.1 (1.4-0.6)	1.1 (1.8-0.4)	1 (1.4-0.75)	0.976
SE (kg)	0.6 (0.9-0.2)	0.7 (1.3-0.4)	0.7 (1-0.4)	0.492
SAB (kg)	0.85 (1.5-0.4)	1.1 (1.8-0.7)	1.2 (2.2-0.7)	0.258
SAD (kg)	0.45 (1-0.2)	0.5 (0.5-0.3)	0.7 (1-0.2)	0.978
SIR (kg)	0.5 (0.5-0.32)	0.65 (1.5-0.5)	0.7 (1-0.47)	0.091
SER (kg)	0.5 (0.8-0.25)	0.55 (1-0.35)	0.8 (1-0.5)	0.326
SPADI in pain (score)	- 7 (4-12)	-10 (4-15)	-6 (4-12.5)	0.622
SPADI functional (score)	-6.8 (2.8-10)	-10 (2.8-13.75)	-6.8 (2.5-10.3)	0.485
SPADI total (score)	-8 (3.2-10.7)	-10.7 (3.4-14.4)	-6.5 (4.2-9.2)	0.346

PR: pain at rest, PDA: pain during activity, JPSF: JPS in flexion, JPSA: JPS in abduction, SF: strength of flexion, SE: strength of extension, SAB: strength of abduction, SAD: strength of adduction, SIR: strength of internal rotation, SER: strength of external rotation, JPS: Joint position sense, SPADI: Shoulder Pain and Disability Index, # $p < 0.05$; Kruskal Wallis test.

DISCUSSION

In the current study, in which we aimed to investigate whether the conservative physiotherapy protocol we applied to SIS patients made a difference in the improvement of pain, range of motion, joint position sense, muscle strength, and shoulder functionality level according to acromion types, it was determined that the treatment results of the study protocol showed differences in range of motion and partially in joint position sense in terms of SIS. In the delta values of flexion joint angles before and after treatment, the type 3 group showed less improvement than the type 1 and type 2 groups. In abduction joint angle, the type 3 group showed less improvement than the type 1 group. Abduction joint position sense showed more deviation in type 1 and type 2 groups than in type 3 groups. It was determined that pain values, muscle strength, and shoulder functionality levels improved after the CP protocol, but acromion morphology had no effect on the improvement in these parameters.

SIS is the most common pathology of the shoulder. Physiotherapy management of SIS includes multiple interventions such as exercise, electrotherapy, advice, and education [19]. Hot packs, cold packs, ultrasounds, conventional TENS, and exercise are also the physical therapy modalities in the conservative treatment of SIS [8]. Many studies have indicated that there

is strong evidence for exercise to reduce pain and improve functionality in short-term follow-up treatment in SIS [20]. In a study that examined the effects of physiotherapy in SIS, it was emphasized that one of the major effects of physiotherapy is pain. Conservative physiotherapy has been shown in randomized controlled studies to improve joint position sense in patients with SIS [2,3]. In addition, previous studies have found that conservative physiotherapy has positive effects on shoulder joint range of motion in SIS patients [8,21]. Sixteen studies were examined by Kromer et al. [21] and they stated that the addition of manual therapy techniques to the treatment gave better results in terms of pain reduction. In the same literature review, it was stated that physiotherapy provides an increase in functionality in some studies, while some do not. In a meta-analysis study by Hanratty et al. [20] was stated that exercise has a small positive effect on muscle strength in short-term treatments of SIS patients. Lombardi et al. [22] who determined that muscle strength increases after a short-term treatment, emphasize that muscle strength develops only in the flexion direction and not in other directions. In our study, all groups showed a decrease in pain at rest and pain in activity, an increase in shoulder joint angles, an increase in shoulder flexion, extension, abduction, internal rotation, and extensional rotation muscle strength values, and significant improvements in shoulder functionality levels after treatment. These results showed that the effectiveness of the CP protocol applied in our study had compatible outcomes with the literature.

A study was stated that the factors increasing the compression on the anterior side of the acromion, especially between the anterior humeral head and the coracoacromial ligament, were due to increased load and calcification in this region. It was emphasized that this situation is important in the formation of the acromion type [23]. Among the acromion types, especially the type 3 form, the acromio-humeral joint space is narrower [24]. Other studies have reported that individuals with type 3 acromion have more SIS symptoms [21, 25]. In the literature, there are studies indicating that acromion type is effective in the occurrence of SIS [5-7]. We found studies examining the relationship between the occurrence of pathologies and acromion type. In particular, it was wondered if the acromion type changed the results in acromioplasty, bursectomy, or in other surgeries [26]. We think that calcifications in the acromion of individuals with type 3 acromion may affect shoulder ROM and proprioception by narrowing the acromio-humeral joint space. In our study, this may be the reason why the type 3 acromion group had less improvement in shoulder flexion angle compared to the type 1 and type 2 groups. In addition, not only shoulder flexion but also shoulder abduction angle increased less in the type 3 group when compared to the type 1 group. In a study, it was stated that shoulder ROM is a determining parameter in improving shoulder proprioception [27]. In our study, we think that proprioception was affected in the same way, in parallel with the fact that the shoulder ROM values of the individuals in the type 3 group improved less than the other groups. This situation explains the fact that the deviation values in abduction joint position sensation after treatment in type 1 and type 2 groups were less than in type 3 groups.

Circi et al. [28] claimed that acromion type does not have an effect on treatment results in patients with SIS. In the same study, it was reported that acromion morphology had no effect on shoulder functionality. In our study, SPADI scores, which we used to evaluate shoulder functionality, showed no difference in the post-treatment change values in all acromion types, similar to that study.

Limitations

The limitations of our study include the lack of distinction between the affected and dominant side, the inability to evaluate shoulder internal and external proprioception, and the lack of a long-term follow-up study.

CONCLUSIONS

In our study, it was concluded that the CP protocol provided significant improvement in pain, ROM, joint position sense, shoulder muscle strength, and shoulder functionality in all acromion types. However, the type 3 acromion structure may be more handicapped in terms of improvements in ROM and proprioception than other acromion types.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The author declared that this study has received no financial support.

Clinical Trial ID: This study is registered as an International Standard Randomised Controlled Trial, number NCT04392934**.**

Ethical Approval: The approval of Non-Interventional Research Ethics Committee of Hasan Kalyoncu University with

the registration number 2019/100 (Date: 01.10.2019). The study permission was taken from Harran University Research and Application Hospital (No: 66063783-622.99)..

Author Contributions: Conseption: B.T., H.D. - Design: B.T., H.D. - Supervision: B.T., H.D.- Fundings: H.D. - Data Collection and/or Processing: B.T., H.D. - Analysis and/or Interpretation: B.T., H.D., Ç.M. - Literature Review: B.T., H.D., Ç.M. - Writing: B.T., H.D., Ç.M. - Critical Review: B.T., H.D., Ç.M.

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How to Cite;

Turhan B, Doğan H, Maden C (2024) Comparison of the Post Treatment Outcomes of A Conservative Physiotherapy Protocol for Subacromial Impingement Syndrome in Terms of Acromion Morphology. Eur J Ther. 30(3):313-321. https://doi.org/10.58600/eurjther1910

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):322-331.
https://doi.org/10.58600/eurjther1931

Original Research

Investigation of the Effects of Remote Online Exercise Training in Individuals Self-Isolating at Home Due to COVID-19 Disease: A Randomized Controlled Study

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Received: 2023-11-13 **Accepted**: 2023-12-19 **Published Online**: 2023-12-19

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This study was presented as an oral presentation at the 1st International / 4th National Health Services Congress held in Isparta on 10-12 June 2022.

ABSTRACT

Objective: Effectiveness of a 4-week telerehabilitation program including thoracic expansion exercises (TEE), non-specific general body exercises (NSGBE), and physical activity recommendations (PAR) which started at quarantine in individuals with acute mild-COVID-19 was investigated in current study.

Methods: This is a randomized controlled study which was performed between May 2021 and February 2022. Adult individuals with acute mild-COVID-19 were randomly grouped as training (TG) (telerehabilitation program under supervision for 3 days/week) and control (CG) (home program including TEE and PAR). Dyspnea (Modified Borg Scale and Modified Medical Research Council Dyspnea Scale), chronic fatigue (Checklist Individual Strength Questionnaire), anxiety and depression (Hospital Anxiety and Depression Scale), balance (Berg Functional Balance Scale) and lower body strength (a 30-s chair stand test) were evaluated remotely in the individuals before and after a 4-week follow-up.

Results: Baseline characteristics and balance scores were similar between groups ($p>0.05$). After 4-week from baseline, there were no significant differences in dyspnea, chronic fatigue, anxiety, depression, balance, and lower body strength between the groups ($p>0.05$). However, as dyspnea, chronic fatigue, anxiety, and depression scores decreased, lower body strength increased significantly within TG after follow-up ($p<0.05$). Dyspnea, chronic fatigue, and anxiety scores decreased while lower body strength increased significantly within CG after follow-up ($p<0.05$).

Conclusion: Dyspnea, severe fatigue, anxiety, and depression are commonly observed in individuals with mild-COVID-19 in the acute period. In these individuals, dyspnea perception, chronic fatigue, anxiety, depression, and functional performance improve after a 4-week light-intensity online tele-program applied either supervised or unsupervised. Mild exercises and PAR are safe and effective in these individuals (Clinical Trial Id: ACTRN12622000121763).

Keywords: Anxiety, COVID-19, Depression, Fatigue, Physical Activity, Telerehabilitation

INTRODUCTION

Individuals with mild-SARS-CoV-2 (COVID-19) have fever, pain, cough, sore throat, and signs of nasal congestion [1,2]. Individuals with COVID-19 may also experience different symptoms including dyspnea, fatigue, muscle pain, and muscle weakness [3] since many systems and organs are directly

affected regardless of disease severity [4]. Moreover, these individuals may be exposed to sleep disturbances, decreased activity endurance, anorexia, pain disorders, and psychological dysfunctions [5]. Diaphragmatic fatigue, respiratory muscle weakness, and cardiopulmonary dysfunction may occur in these individuals due to immobilization for a long time due to COVID-19, as well [5].

In the days when the pandemic first started, approaches that increase respiratory work and distress (airway clearance techniques, thoracal expansion exercises (TEE), exercise training, respiratory muscle training, etc.) were not recommended for individuals with acute COVID-19 [1]. The rapidly increasing incidence of COVID-19 and the remarkable increase in the probability of transmission by asymptomatic carriers are important reasons of this recommendation [1]. However, as it is now known, approximately 33.2% of individuals with COVID-19 continue to experience many symptoms such as heart attack, limitations in daily living activities, and difficulties in walking, exercise, concentrate or breathing even after the illness has passed [6]. Therefore, nowadays, it is recommended to consider and change rehabilitation approaches such as physical activities, exercises, and active mobilization in these patients at the most appropriate time, based on the severity of COVID-19 and underlying chronic diseases which are also suitable for individuals with mild to moderate severity COVID-19 in the acute period [1,7]. It may be preferable to perform all these exercises at home with or without supervision through telerehabilitation (real-time video-conference technology, training videos, video calls, phone calls, etc.) to minimize COVID-19 virus contact [7-13]. Effectiveness and feasibility of telerehabilitation programs consisting of TEE, strengthening, and/or relaxation exercises in the acute and post-acute periods of COVID-19 have been confirmed by new studies [10,11,14-18]. It is seen that the duration of exercise programs conducted in the acute period of COVID-19 are during quarantine period [10-13]. On the other hand, considering that the symptoms continue for a while after the recovery of COVID-19, to reveal effectiveness of exercise training, which started in the acute period of COVID-19 and continued for the next 3 weeks, is important. Therefore, this study aimed to investigate effects of 4-week telerehabilitation program consisting of TEE, non-specific general body exercises (NSGBE), and physical activity recommendations (PAR) on dyspnea, fatigue, anxiety, depression, balance, and lower body strength in individuals with acute mild-COVID-19 at home quarantine.

Main Points;

- A 4-week comprehensive telerehabilitation program is safe and feasible in individuals with acute mild-COVID-19
- Many individuals with acute mild-COVID-19 have dyspnea, severe fatigue, anxiety, and depression.
- Telerehabilitation program including thoracic expansion exercises, physical activity recommendations and/or non-specific general body exercises has important healing effects on dyspnea perception, chronic fatigue, anxiety, and lower body strength in individuals with acute-COVID-19.
- When non-specific general body exercises were added to thoracic expansion exercises and physical activity recommendations, depression also decreased in individuals with acute-COVID-19.

MATERIALS AND METHODS

Study Design

The study was planned as a prospective, randomized, controlled, parallel and single blind (individuals with COVID-19) which was conducted at Izmir Democracy University Physiotherapy and Rehabilitation Department between May 2021 and February 2022. Eligible individuals were blinded and randomly allocated to training (TG) or control (CG) groups through a website-based randomization by GB. The individuals were started to be evaluated on the 4-6th day of quarantine by ASKK and performed exercise 7th day of the quarantine by EŞ. Measurements (ASKK) and exercises (EŞ) were performed by different physiotherapists. In line with the possibilities of the individuals, all evaluations and exercise training were performed remotely as one-to-one interview through video phone calls using WhatsApp and/or online videoconference using Microsoft teams. All individuals with mild-COVID-19 were followed-up at home as doing exercise training during 4-week by a physiotherapist. Primary outcome was anxiety. Secondary outcomes were dyspnea, fatigue, depression, balance, and functional performance. Izmir Democracy University Non-Interventional Clinical Research Ethics Committee (date: 23/03/2021, number: 2021/03-10) approved the study, that followed principles of Declaration of Helsinki. Informed consent forms were obtained from all individuals with COVID-19.

Study Population

Individuals diagnosed with acute mild-COVID-19 and followed-up at home were included between May 2021 and February 2022 and invited to participate in the study through social media and acquaintances of the researchers. Inclusion criteria were; volunteering, being adult, being able to do exercises with good cooperation, having a technological device such as smartphone, computer, iPad, or laptop, etc. where evaluations and exercises could be applied, having a positive Polymerase Chain Reaction (PCR) test result, being compatibility with COVID-19 infection as a result of chest X-ray or lung tomography despite a negative PCR test result, and being diagnosed with acute mild-COVID-19 and followed up by self-isolation at home. Exclusion criteria were; having any unstable angina pectoris, uncompensated heart failure, previous myocardial infarction, uncontrolled diabetes, hypertension above 180/110 mmHg, severe neuropathy, chronic orthopedic disorder, neurological disorders, severe psychiatric illness and/or cooperation problem that could prevent exercises, recovering from COVID-19, being pregnant, having severe muscle spasm, involuntary weight loss, and/or symptom incompatibility, or having severe dyspnea, cyanosis, and/or hemoptysis.

Exercise Training

Comprehensive telerehabilitation program containing TEE, NSGBE, and PAR was applied to TG via one-to-one online video phone call, phone voice call and/or online videoconferencing with Microsoft Teams, depending on the individuals' opportunities and availability, for 30-45 minutes/day, 3 days/week and totally 4-week. TEE consisted of a cycle of deep breathing by placing hands on lower ribs of the individual, holding breath for 3 seconds at total lung capacity, and exhaling all breathe slowly. After individuals had performed incessantly this cycle 3 times, they rested with 3-4 calm breathings all of which were repeated as 10 repetitions in a session. Individuals in TG were asked to do TEE session 4 times per a day, and one TEE session was administered under supervision in sessions held by online conference. NSGBE using body weight and/or light weights was performed under supervision for 3 days/week and 4 weeks by video calls and online video conferencing. These exercises generally consisted of general body and stretching exercises which were started from the simplest form and progressed by increasing number of repetitions and/or weights (Table 1). The PAR was recommended as 2-3 minutes of taking short walks at home every 30 minutes during the day except for sleep time. Moreover, a home program including TEE, same NSGBE and PAR was given in TG for other days of the week. Verbal confirmation at end of online sessions was used to monitor adherence to the home program in TG.

Table 1. Non-specific general body exercises

Exercise type	Repeat time, frequency, intensity, progression for each type of exercise
Supine position 1. Bridge 2. Sit-ups **Prone position** 1. Hip extension 2. Upper body extension **Crawling position** 1. Hip and knee extensions 2. Elbow extension and shoulder flexion **Standing position** 1. Squat 2. Forward lunge	**1st week:** 5 repetitions/set, 1 set/day, 7 days/week (3 days supervised), no weight. **2nd week:** 8-10 repetitions/set, 1 set/day, 7 days/week (3 days supervised), no weight. **3rd week:** 15 repetitions/set, 1 set/day, 7 days/week (3 days supervised), with 0.5-1 kg weight (water bottle, package, sandbag/dumbbell if any, etc.). **4th week:** 20 repetitions/set, 1 set/day, 7 days/week (3 days supervised), with 0.5-1 kg weight (water bottle, package, sandbag/dumbbell if any, etc.).
Sitting position 1. Hamstrings stretching **Supine position** 1. Latissimus dorsi stretching 2. Lumbar extensors stretching	**From 1st week to 4th week:** 30 second stretching, 10 second relaxing, 3 repetitions/set, 1 set/day, 7 days/week (3 days supervised).

A 4-week home program including TEE and PAR was given to CG. These individuals received only one session by phone video call and/or online videoconferencing with Microsoft Teams in a total 30-45 minutes, and the program was taught in this session. The individuals were asked to do TEE exercise for 4 times/day and every day. Moreover, same PAR was also given to these individuals. Verbal confirmation via SMS text reminders at end of every week was used to monitor adherence to the program. After 4 weeks of follow-up, it continued to be applied to CG who wants NSGBE.

Measurements

The measurement of the first individual included in the study was performed on May 1, 2021. The final measurement of the

last individual included in the study was made on February 28, 2022. A measurement session of an individual was completed within approximately 30-60 minutes, considering the fatigue level of the individual. All individuals were evaluated to measure demographic characteristics, dyspnea, chronic fatigue, anxiety and depression, balance, and lower body strength before and after 4-week follow-up. Individuals responded to all questions administered by physiotherapists during online interviews.

The demographic characteristics were recorded. Dyspnea perception was evaluated using Modified Borg Scale (MBS) and Modified Medical Research Council Dyspnea Scale (MMRCDS). The MBS is scored between 0 (no dyspnea) and 10 (extremely severe dyspnea) which shows severity of dyspnea [19]. The MMRCDS is scored between 0 (no dyspnea) and 4 (almost complete incapacity due to dyspnea) which shows presence of daily living activities [20]. Chronic fatigue perception in the last 2 weeks was assessed using Checklist Individual Strength Questionnaire [21] consisting of totally 20 statements and 4 aspects [subjective experience of fatigue (8-statement), concentration (5-statement), motivation (4-statement), and physical activity (3-statement)]. Each statement is scored as straight or reverse through a 7-point Likert scale (from 1 "yes true" to 7 "not true") [22]. Cut-off point for severe fatigue is ≥40 [23]. Anxiety and depression during past week were evaluated with Hospital Anxiety and Depression Scale [24]. Out of 14 questions, 7 measures anxiety (anxiety subscale), and 7 measures depression (depression subscale). The answers are evaluated on a four-point Likert scale and scored between 0 and 3. For each subscale, the lowest score is 0 and the highest score is 21. Cut-off scores are 10 points for anxiety and 7 points for depression subscales [25]. To evaluate balance, Berg Functional Balance Scale was used in current study containing 14 movements reflecting everyday life [26]. Each movement is scored from 0 (unable to perform) to 4 (normal performance). The highest score is 56 points which shows full postural control [27]. A 30-s chair stand test was used to determine lower body strength and functional mobility. The individual sits in a chair with no back support, arms crossed over trunk which is initial seated position. Next, the individual stands and sits consecutively for 30 seconds. Total number of correct stands during this period was recorded. The higher number of repetitions indicates better physical performance [28].

Statistical Analyses

To determine mean difference in anxiety scores (7.5) between two independent groups for an α value of 0.05, a power of 80%, at least 15 individuals were calculated for each group [14] through GPower program (G*Power 3.0.10 system, Franz Faul, Universität Kiel, Germany) [29]. Statistical analyzes were conducted using the SPSS 15.0 program. Descriptive analyzes were offered using frequency (n), percentage (%), median, interquartile range (IQR), mean (x), and standard deviation (sd). Variables between groups were compared using Mann-Whitney U and Chi-square tests. Pre- and post-program variables within each group were compared using Wilcoxon test. Difference variables of pre- and post-program values were compared using Mann-Whitney U test between groups. Effect size d (Cohen's d) values were calculated and interpreted as small (0.20), moderate (0.50) and large (>0.80) effect sizes. Post-hoc statistical powers were calculated and presented as 1-β. The probability of error was accepted as $p \leq 0.05$.

RESULTS

Out of 33 individuals with acute mild-COVID-19, 13 in TG and 7 in CG completed the study (Figure 1). None of the individuals had any balance problems before or after the program.

Before 4-week program: Dyspnea during daily living activities existed in 9 (69.2%) individuals in TG and 4 (57.1%) individuals in CG; severe fatigue was experienced by 8 (61.5%) individuals in TG and 3 (42.9%) individuals in CG; 4 (30.8%) individuals in TG had anxiety; 6 (46.2%) individuals in TG and 3 (42.9%) individuals in CG had depression (Figure 2, $p>0.05$). Baseline characteristics were similar between groups (Table 2-3, $p>0.05$).

After 4-week program: Dyspnea during daily living activities existed in 4 (30.8%) individuals in TG and 2 (28.6%) individuals in CG; severe fatigue was experienced by only 1 (7.7%) individual in TG; 2 (15.4%) individuals in TG had anxiety (Figure 2, $p>0.05$). No significant differences were found in dyspnea perception (MBS score: effect size= 0.83, 1-β=0.40) (MMRCDS score: effect size d= 0.41, 1-β=0.13), chronic fatigue (CIS total score: effect size d= 0.29, 1-β=0.09), anxiety (effect size d: 0.14, 1-β=0.06), depression (effect size d: 0.07, 1-β=0.05), balance, and lower body strength (effect size d: 0.43, 1-β=0.15) between the groups (Table 4, $p>0.05$). Within TG, dyspnea perception, chronic fatigue, anxiety, and depression scores significantly decreased while lower body strength significantly increased after 4-week (Table 4, $p<0.05$). Within CG, dyspnea, chronic fatigue, and anxiety significantly decreased as lower body strength significantly increased after 4-week (Table 4, $p<0.05$). No change occurred in balance score within both groups (Table 4, $p>0.05$).

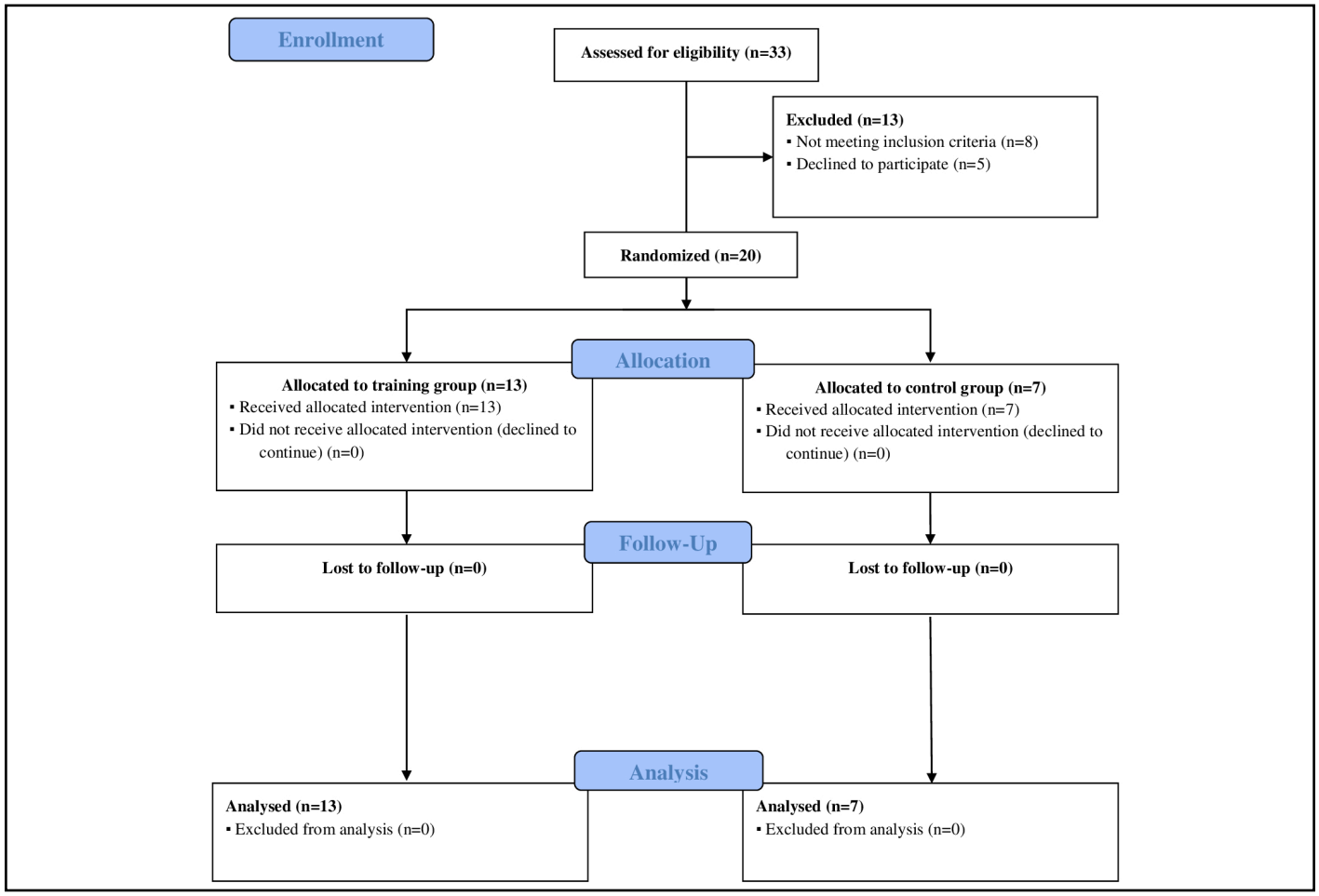

Figure 1. Consort flow diagram of the study.

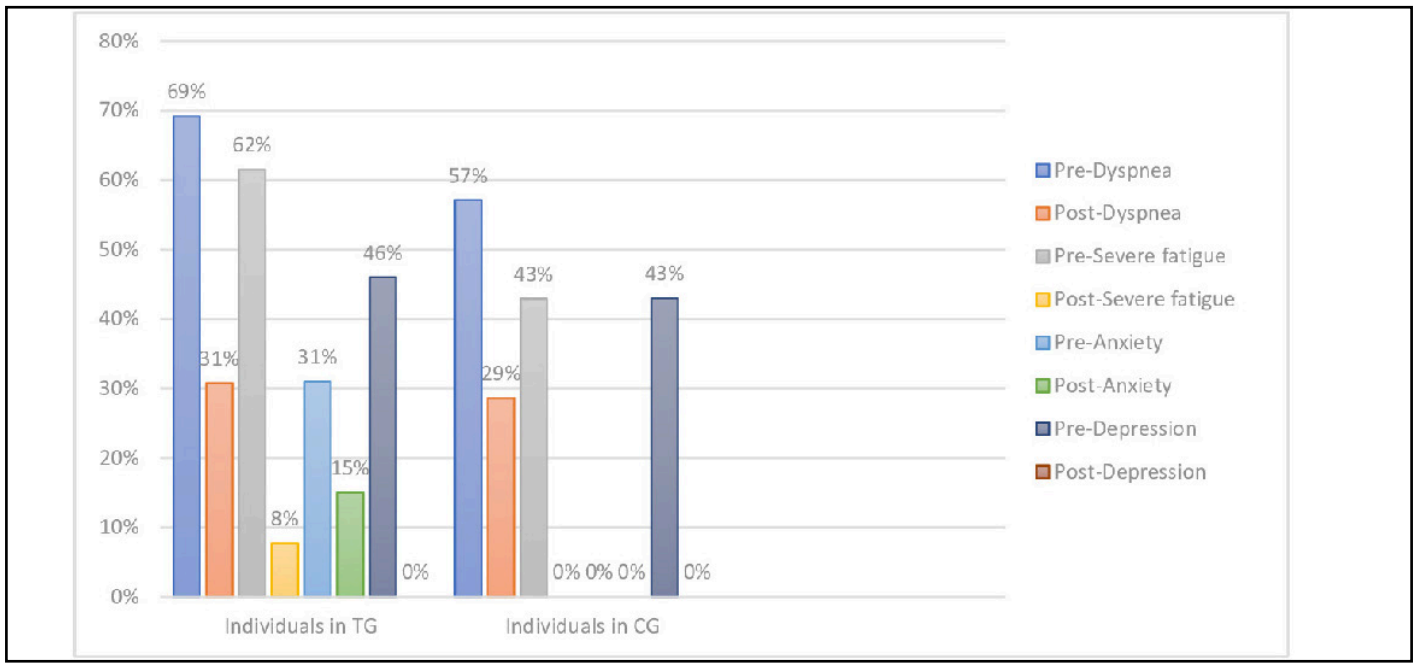

Figure 2. Pre-post-program rates of dyspnea, severe fatigue, anxiety, and depression in the groups.

Table 2. Demographic characteristics of the groups

	TG (n=13) x±sd	CG (n=7) x±sd	p value
Age (year)	31.77±5.76	29.57±7.55	0.474
Weight (kg)	58.62±8.20	75.29±25.54	0.139
Height (m)	1.68±0.09	1.72±0.14	0.440
BMI (kg/m^2)	20.86±3.19	24.88±5.94	0.062
Female (n (%))	11 (84.6%)	4 (57.1%)	0.290
Male (n (%))	2 (15.4%)	3 (42.9%)	
Presence of exercise habits (n (%))	4 (30.8%)	2 (28.6%)	1.000
Presence of chronic illness (n (%))	3 (23.1%)	2 (28.6%)	1.000

kg: kilogram, m: meter, n: frequency, %: percent, TG: training group, CG: control group, x: mean, sd: standard deviation. Chi-square test, $^{\#}p<0.05$; Mann-Whitney U test, *p<0.05.

Table 3. Comparison of the values of the groups before online program

	TG (n=13)		CG (n=7)		U value	p value
	x±sd	median (IQR)	x±sd	median (IQR)		
MBS (0-10)	1.38±1.71	1 (3)	2.43±2.07	3 (4)	32	0.267
MMRCDS (0-4)	1±0.91	1 (2)	0.71±0.76	1 (1)	38	0.523
CIS total score (20-140)	90.08±22.93	93 (22.5)	81±11.24	82 (24)	24.5	0.096
Subjective fatigue (8-56)	39.62±10.28	42 (11)	35.86±7.82	33 (17)	30.5	0.234
Concentration (5-35)	20.46±6.65	21 (8)	18.57±8.58	21 (17)	40	0.661
Motivation (4-28)	15.92±6.58	18 (11)	12.29±3.55	12 (5)	27	0.141
Physical activity (3-21)	14.08±4.15	14 (4)	14.29±3.09	15 (2)	40.5	0.687
HAD total score (0-42)	14.39±8.62	13 (5.5)	9.57±5.19	8 (9)	30	0.217
Anxiety (0-21)	8±5.87	8 (7)	4.43±2.51	4 (4)	26	0.120
Depression (0-21)	6.38±4.37	5 (9)	5.14±2.85	4 (6)	37.5	0.524
Berg Balance Scale (0-56)	56	56	56	56	45.5	1.000
30-s chair stand test (n)	14±3.61	14 (5)	13.29±4.19	11 (4)	35	0.402

MBS: Modified Borg scale, MMRCDS: Modified Medical Research Council Dyspnea scale, CIS: Checklist Individual Strength questionnaire, HAD: Hospital Anxiety and Depression scale, n: frequency, TG: training group, CG: control group, x: mean, sd: standard deviation, IQR: Interquartile range. Mann-Whitney U test, *p<0.05.

Table 4. Comparison of the values of the groups before and after program

	TG (n=13)			CG (n=7)			Between groups p value
	Before program	After program	Within-groups p value	Before program	After program	Within-groups p value	
	x±sd median (IQR)	x±sd median (IQR)		x±sd median (IQR)	x±sd median (IQR)		
MBS (0-10)	1.38±1.71 1 (3)	0.77±1.09 0 (2)	0.121	2.43±2.07 3 (4)	0.43±0.79 0 (1)	#**0.042**	0.084
MMRCDS (0-4)	1±0.91 1 (2)	0.31±0.48 0 (1)	#**0.014**	0.71±0.76 1 (1)	0.29±0.49 0 (1)	0.083	0.482
CIS total score (20-140)	90.08±22.93 93 (22.5)	44.31±20.04 39 (30)	#**0.002**	81±11.24 82 (24)	28.71±11.56 20 (18)	#**0.018**	0.721
Subjective fatigue (8-56)	39.62±10.28 42 (11)	18.31±10.55 16 (13)	#**0.002**	35.86±7.82 33 (17)	11.71±4.92 8 (7)	#**0.018**	0.781
Concentration (5-35)	20.46±6.65 21 (8)	12.69±6.16 11 (10)	#**0.003**	18.57±8.58 21 (17)	7.71±3.64 5 (5)	#**0.043**	0.525
Motivation (4-28)	15.92±6.58 18 (11)	7.15±2.61 6 (5)	#**0.002**	12.29±3.55 12 (5)	5±1.29 4 (2)	#**0.018**	0.605
Physical activity (3-21)	14.08±4.15 14 (4)	6.15±3.6 5 (4)	#**0.004**	14.29±3.09 15 (2)	4.29±1.89 3 (4)	#**0.018**	0.551
HAD total score (0-42)	14.39±8.62 13 (5.5)	7.31±4.85 8 (8.5)	#**0.008**	9.57±5.19 8 (9)	2.29±2.81 1 (5)	#**0.034**	0.842
Anxiety (0-21)	8±5.87 8 (7)	5.23±3.52 5 (6)	#**0.045**	4.43±2.51 4 (4)	1.14±2.27 0 (2)	#**0.042**	0.605
Depression (0-21)	6.38±4.37 5 (9)	2.08±1.75 2 (3)	#**0.003**	5.14±2.85 4 (6)	1.14±1.35 1 (3)	0.062	0.937
Berg Balance Scale (0-56)	56	56	1.000	56	56	1.000	1.000
30-s chair stand test (n)	14±3.61 14 (5)	15.85±3.05 16 (5)	#**0.054**	13.29±4.19 11 (4)	16.14±3.85 15 (4)	#**0.014**	0.372

MBS: Modified Borg scale, MMRCDS: Modified Medical Research Council Dyspnea scale, CIS: Checklist Individual Strength questionnaire, HAD: Hospital Anxiety and Depression scale, n: frequency, TG: training group, CG: control group, x: mean, sd: standard deviation, IQR: Interquartile range. Wilcoxon test, #p<0.05; Mann-Whitney U test, *p<0.05.

DISCUSSION

A 4-week safe and feasible comprehensive telerehabilitation program were applied to individuals self-isolating at home due to acute mild-COVID-19 in this preliminary randomized controlled study which is the first study conducted during acute and subacute period of mild-COVID-19, to our knowledge. Before this program, while dyspnea, severe fatigue, anxiety, and depression existed in many individuals with acute COVID-19, balance problem was not observed in these individuals. After the program, while dyspnea, severe fatigue, and anxiety continued to be observed in some individuals, the individuals had no depression and balance problem. This tele-program has considerably healing effects on dyspnea perception with moderate-large effect size, chronic fatigue, anxiety, and lower body strength in individuals with acute-COVID-19 regardless of the practice of NSGBE. When NSGBE were added to telerehabilitation program, depression also decreased in the individuals. No complications were observed secondary to the exercises.

Healing effects of various rehabilitation approaches such as pulmonary rehabilitation, telerehabilitation, progressive muscle relaxation, low-intensity aerobic exercises, strengthening

exercise, and cognitive behavioral therapy on pulmonary function, muscle strength, exercise capacity, Kinesio phobia, fatigue, mood, sleep quality and/or quality of life are still being revealed in individuals with COVID-19 at the acute or post-acute periods [10,11,14-18]. In line with our results, healing effects of TEE and strength exercises applied as 14-day telerehabilitation versus a CG on fatigue, dyspnea, exercise capacity, and lower body strength were revealed in individuals with acute mild-COVID-19 [10]. Moreover, improvements in dyspnea and exercise capacity were more pronounced in TEE group and no complication after exercise programs was found [10]. Therefore, Rodríguez-Blanco et al. recommend combining TEE and strength exercises for the management of these patients, as conducted in our study [10]. Liu et al. also investigated 5-day effectiveness of progressive muscle relaxation and deep breathing exercises (Jacobson's relaxation techniques, 20-30 min/day, 5 consecutive days) versus a CG on anxiety and sleep quality in patients with acute-COVID-19 isolated at hospital [11]. After training, anxiety and sleep quality considerably improved in exercise group compared to controls in parallel with our results [11]. In another study of Rodriguez-Blanco et al., feasibility and effectiveness of a 1-week therapeutic muscle conditioning exercise through telerehabilitation versus a CG on exercise capacity, dyspnea, and lower body strength in patients with acute mild to moderate-COVID-19 were searched [12]. In consistent with our results, this program including muscle toning exercise is effective, safe, and feasible in patients with acute COVID-19 isolating at home or hospital, which improves all parameters with a good patient adherence (90%) compared to the CG [12]. Gonzalez-Gerez et al. exposed same effectiveness of 1-week pulmonary rehabilitation based on TEE through telerehabilitation versus a CG on same outcomes in these patients [13]. Since individuals in CG did not receive exercise in these studies [10-13], the difference in TG might have been determined better compared to CG inconsistent with our results. On the other hand, these studies [10-13] have been consistently verified effectiveness and feasibility of various online remote exercise trainings consisting of TEE, strengthening, and/or relaxation exercises in the acute period of COVID-19 regardless of exercise duration. The superiority of our study compared to these studies was that both longer exercise duration (starting from the quarantine period and completing at the end of a 4-week follow-up) and application of more comprehensive exercises to both groups. Moreover, in current study, our individuals in TG were followed-up in one-to-one sessions for 3 days/week and totally 4-week unlike other studies [10-13]. However, we could not reach targeted sample size due to constantly changing number of quarantine days and rules. The quarantine period, which was previously 14 days for close contacts of COVID-19 patients, was updated to 10 days. Now this period has been reduced to 5 days even further. As all these changes directly affected the methodology of our study, we could not continue the study. Ultimately, although differences between TG and CG were not shown in our study, our study is of great importance in terms of demonstrating safe and effective applicability of more comprehensive remote online exercises and physical activities beginning in the acute phase of COVID-19 and continuing in the subacute phase. In the light of all these findings, we suggest investigating effects of long-term programs that start in the acute phase of COVID-19 and continue in the subacute/chronic phase on long follow-up periods.

Limitations

Our main limitation is that we could not reach a sufficient sample size due to reduction of the severe adverse effects of COVID-19 over time, and/or the continuous change of the COVID-19 quarantine rules from May 2021 to February 2022. Therefore, we could not obtain effectively more positive changes in dyspnea, fatigue, mood, and lower body strength demonstrating the superiority of TG in the current study. Future work should be planned with this in mind.

CONCLUSIONS

Following 4-week supervised telerehabilitation program, important improvements experienced by individuals with acute mild-COVID-19 self-isolating at home are reductions in dyspnea perception, chronic fatigue, anxiety, and/or depression and better functional performance. Moreover, when the exercises including TEE and PAR are applied as a home program in individuals with acute mild-COVID-19 who cannot follow a strictly supervised rehabilitation program, same improvements excluding decreased depression are seen in these individuals. Mild severity telerehabilitation program, TEE and PAR are safe and effective in individuals with mild-COVID-19.

Acknowledgments: This study was presented as an oral presentation at the 1st International / 4th National Health Services Congress held in Isparta on 10-12 June 2022.

Conflict of interest: It is declared that there is no conflict of interest in current study.

Informed Consent: Informed consents from all individuals were obtained.

Funding: None.

Ethical Approval: The ethical approval (Izmir Democracy University Non-Interventional Clinical Research of the Ethics Committee, date: 23/03/2021, number: 2021/03-10) existed.

Author Contributions: Conception: GB, ASKK - Design: GB, ASKK - Supervision: GB - Fundings: GB -Materials: GB, ASKK - Data Collection and/or Processing: GB, ASKK, EŞ - Analysis and/or Interpretation: GB - Literature: GB, ASKK - Review: GB, ASKK, EŞ - Writing: GB, ASKK, EŞ - Critical Review: GB, ASKK, EŞ.

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How to Cite;

Bargı G, Kızılırmak Karataş AS, Şahin E (2024) Investigation of the Effects of Remote Online Exercise Training in Individuals Self-Isolating at Home Due to COVID-19 Disease: A Randomized Controlled Study. Eur J Ther. 30(3):322-331. https://doi.org/10.58600/eurjther1931

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):332-339.
https://doi.org/10.58600/eurjther1935

Original Research

Variation of Wormian and Inca Bones in Adult Skulls

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Received: 2023-11-21 **Accepted**: 2024-01-22 **Published Online:** 2024-01-29

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ABSTRACT

Objective: Irregular and abnormal small additional bones called Wormian bones can be encountered between the skull bones. This study aimed to investigate the incidence, topographical distribution, morphology, and interrelationship of the Wormian and Inca bones in Central Anatolia Region dry adult skulls.

Methods: In the study, 119 adult skulls were examined. The location and frequency of additional bones (Wormian) in the sutures in the cranium were determined. Skulls with Inca bones were identified. The Inca bones were typified in accordance with the literature and their dimensions in the transverse and sagittal axis were measured with a digital caliper.

Results: Wormian bone was present in 33 of 119 adult skulls (27.7%). Of the 33 bones, 22 were detected in the male (66.66%) and 11 female (33.34%) skulls. The locations of the Wormian bones in the order of decreasing incidence were the lambdoid suture (16.0%, 19/119), pterion (16.0%, 19/119), lambda (7.6%, 9/119), asterion (2.5%, 3/119), and bregma (1.7%, 2/119). Nine Inca bones were found in the lambdoid region (27.3%, 9/33). Six of these bones (66.7%) were in the male skull. We found that two of these bones were incomplete lateral asymmetric, two were complete symmetric bipartite, two were incomplete asymmetric bipartite and three were incomplete median type. We found that 13 (10.9%) of the skulls in the study had metopic sutures and 0.8% had craniosynostosis. When the craniums with metopic suture were evaluated, it was found that 8 of them (61.5%) had additional bone. 50% of the Wormian bones were found in the lambdoid suture.

Conclusion: It has been found that the incidence of Wormian bone increases with suture variations. It was determined that the frequency of Inca bone variation may vary depending on regional differences.

Keywords: Morphometry, Inca Bone, Variation, Wormian Bone.

INTRODUCTION

The skull consists of a total of 22 bones, eight in neurocranium and fourteen in viscerocranium. These bones join via cranial sutures [1, 2]. Wormian bones are a large number of irregular, accessory, and abnormal small suture bones located between the skull bones. It differs from person to person in size, shape, number, and thickness. These bones are named according to the fontanelles, the ossification center or the sutures they are in. Human anatomy, neurosurgery, physical anthropology, forensic medicine, craniofacial surgery and radiology are interested in Wormian bone [2, 3]. Anatomical knowledge of suture bones is clinically important because their presence is often used as a descriptive marker of some congenital disorders, particularly bony dysplasia [2].

Inca bone is one of the accessory bones in the cranium and is considered variant of normal [4, 5]. Inca bone is one of the developmental cranial variations with a striking feature; one or occasionally more isolated bones in the upper squama of the occipital bone. Inca bones can be divided by longitudinal sutures and can be bipartite, tripartite, or multipart [6-8].

The variability in Inca bone frequency has been studied in major human populations around the world. Inca bone has a definite anthropological value as an epigenetic trait in racial differentiation [9]. In contrast, the results of Togersen's genealogical research showed that the Inca bone is inherited in an autosomal dominant way, with 50% invasiveness [10]. The Deol and Truslove study found that the appearance of Inca bones in mice is subject to intense genetic control [11].

Morphometric and morphological features of Inca and Wormian bones are important to neurosurgeons, clinicians investigating child abuse, anthropologists, anatomists and forensic experts [12, 13]. Variations of the sutures and sutural bones can be easily misdiagnosed with fractures of related bony regions in unconscious patients with multiple traumas. In case of trauma to the cranium, Wormian bones may be confused with skull fracture on X-rays, causing misdiagnosis and incorrect intervention [7, 14]. Inca bones can be used for personal identification in forensic medicine by comparing pre-mortem and post-mortem radiographs [8].

Main Points:

- Wormian bones were more common in skulls with metopic sutures.
- An increased incidence of Wormian bone has been found in suture variations. Half of the Wormian bones were located in the lambdoid suture.
- Inca bone variation was more common in male skulls.

Although Wormian and Inca bones are quite common, they are poorly reported. In this study, it was aimed to investigate the Wormian and Inca bones variations in adult skulls living in Central Anatolia and to contribute them to the literature.

MATERIALS AND METHODS

In the research, 119 adult skulls were examined. Skulls were obtained from the bone collection at Erciyes University Faculty of Medicine in the Anatomy Laboratory. Skulls with damaged or deformed integrity were not included in the research. Detection of Wormian bones in the cranium and all other findings was done by a two-person team to avoid individual bias and two measurements were taken to reduce the error rate, and the average of these measurements was considered. As a result of the discussions, the bones were noted according to where they were found. The averages of the results were taken into account. Additionally, the lambdoid region was examined for Inca bones. The sex determination of the skulls with Wormian bone was performed using the method suggested by Buikstra and Ubelaker [15]. In addition, the distribution of these bones by sex was determined.

The detected Inca bones were classified and measured in two axes (sagittal-transverse). A digital caliper (Mitutoyo 200 mm Digital Caliper, Mitutoyo Co., Kanagawa, Japan) with 0.01 millimeter (mm) precision was used for measurements. The width and length of the Wormian bones detected at bregma and asterion points were also measured. The types of Inca bones were determined according to the work of Hanihara et al. [9]. In addition, all skulls were evaluated for metopic suture development.

Statistical Analysis

The data were tabulated in a Microsoft Excel worksheet and the analysis of the data was performed using SPSS 22.0 (IBM Corp., Armonk, NY) package program. The results of measurements are given as mean, standard deviation (SD), percentage of presence, and minimum and maximum values.

RESULTS

Findings showing the localization of Wormian and Inca bones are included in Table 1. Morphometric measurements of Wormian bones in bregma and asterion are given in Table 2.

Data about the dimensions of the Inca bone (n=9) were obtained by measuring in transverse and sagittal axes found to be 27.46 ± 13.26 and 43.05 ± 25.72 mm, respectively. The detected Inca bones were typed in accordance with the literature. The findings are in Table 3 and **Figure 1.**

In addition to these, metopic sutures and craniosynostosis findings in the skulls were also evaluated. Thirteen (10.9%) metopic suture and one (0.8%) craniosynostosis were detected in 119 skulls (Figure 2). When the craniums with metopic suture were evaluated, it was found that 8 of them (61.5%) had additional bone. It was observed that one of these bones (12.5%) was in the bregma, 1 (12.5%) was in the asterion, four of them were in the lambdoid suture, and two of them were in the lambdoid region (Figure 3).

Both Inca bones and other Wormian bones were more common in males than females (except the Bregma area). It was determined that the incidence of metopic suture was not related to sex. Inca bone was most common in the central region, and Wormian bones in the lambdoid suture were most common on the left. The distribution and localization of Wormian bones, Inca bones, and metopic suture by sex are shown in Table 4.

Table 1. Wormian bone and Inca bone distribution ratio in all bones examined

Wormian Bone Presence	Location	Number (n)	%
Present	Lambdoid suture	19	16.0
	Lambda (Inca bone)	9	7.6
	Bregma	2	1.7
	Asterion	3	2.5
	Total	33	27.7
Not	-	86	72.3
All examined bones		119	100.0

Table 2. Morphometric measurements of Wormian bones in bregma and asterion (mm)

	Bregma diameters		Asterion diameters			
Measurements	Transverse (n=2)	Sagittal (n=2)	Transverse (right) (n=3)	Sagittal (right) (n=3)	Transverse (left) (n=3)	Sagittal (left) (n=3)
	11.88 (4.69-19.08)	27.98±0.13	13.19±0.95	23.20 (9.64- 31.49)	13.42±0.57	22.90 (12.01-27.41)

Values are expressed as mean ± SD and the median (first-third quartiles).

Table 3. Distribution of variations of Inca bones

Type of Inca bone	Number (n)	%
Incomplete lateral asymmetric (Inca bone laterale dextrum)	2	22.22
Complete symmetric bipartite (Inca bone bipartitum)	2	22.22
Incomplete asymmetric bipartite (Inca bone duplex asymmetricum)	2	22.22
Incomplete median (Inca bone centrale (medianum))	3	33.34
Total	9	100

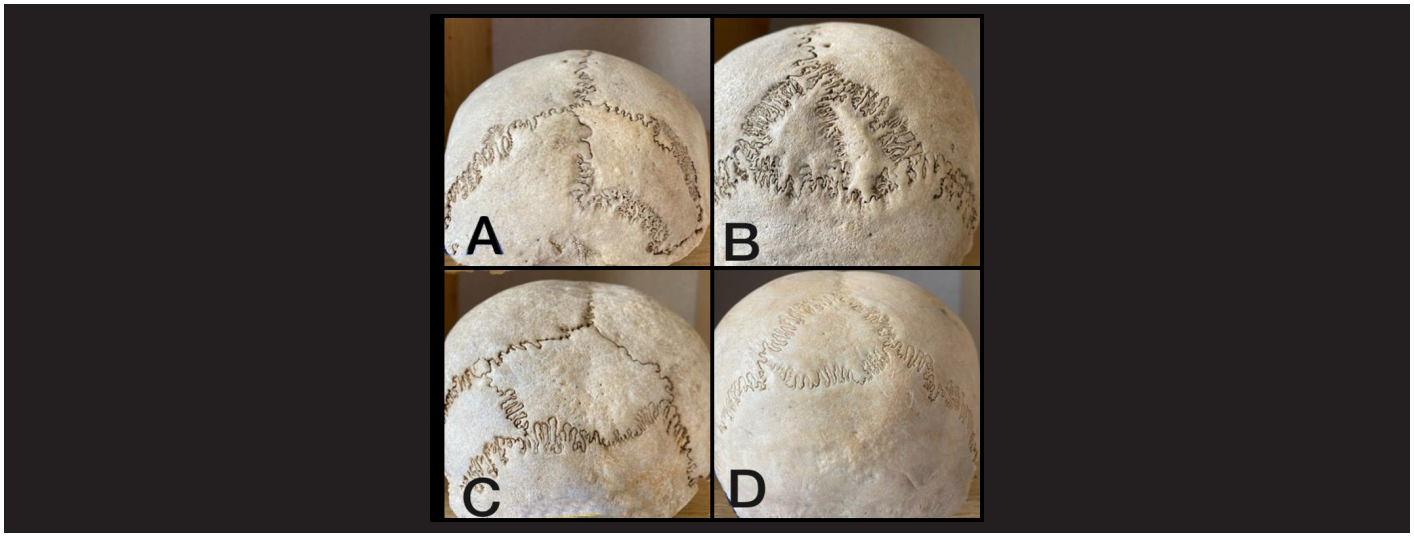

Figure 1. A. Incomplete lateral asymmetric, B. Complete symmetric bipartite, C. Incomplete asymmetric bipartite, D. Incomplete median

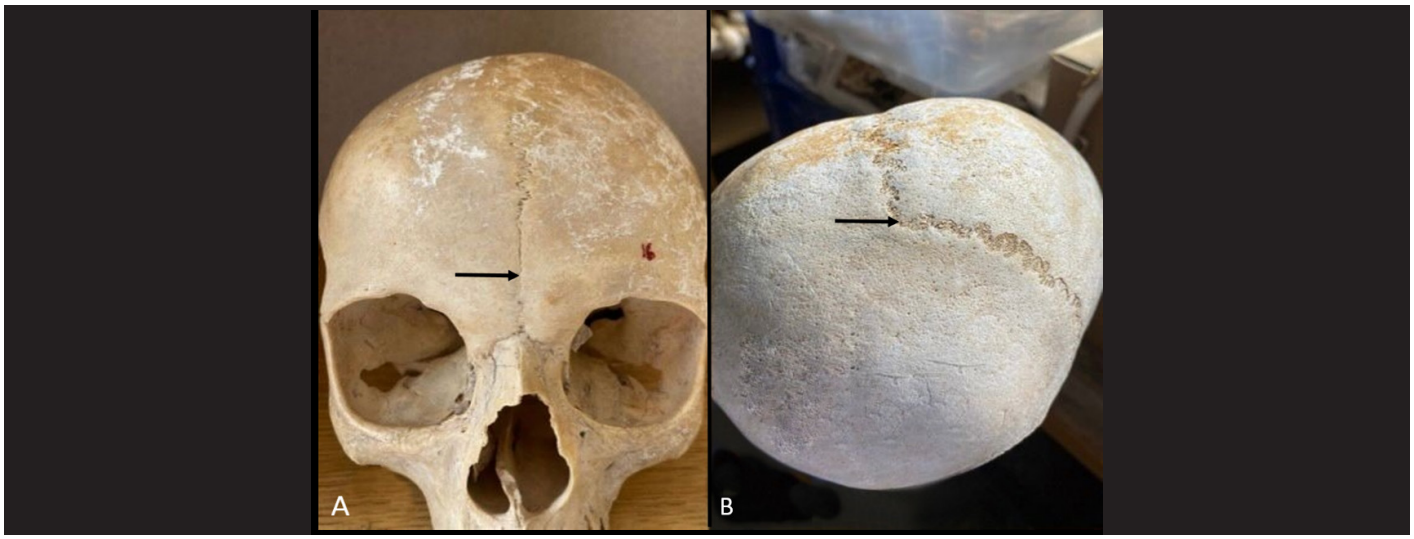

Figure 2. A. Metopic suture, B. Craniosynostosis

Figure 3. Wormian bones and Inca bones accompany the metopic suture skull. A, B, C: Front view of the cranium, D (Inca bone), E (Asterion), F (Bregma).

Table 4. Distribution of Wormian bones, Inca Bone and metopic suture by sex

		Metopic suture	Lambdoid suture	Inca Bone	Bregma	Asterion
Gender						
	Female	7 (53.8%)	7 (36.8%)	3 (33.3%)	1 (50%)	0 (0%)
	Male	6 (46.2%)	12 (63.2%)	6 (66.7%)	1 (50%)	3 (100%)
	Total	13 (100%)	19 (100%)	9 (100%)	2 (100%)	3 (100%)
Location						
	Centre		3 (15.8%)	4 (44.4%)	2 (100%)	0 (0%)
	Right and Left		5 (26.3%)	1 (11.1%)	0 (0%)	3 (100%)
	Right		4 (21.1%)	1 (11.1%)	0 (0%)	0 (0%)
	Left		7 (36.8%)	3 (33.3%)	0 (0%)	0 (0%)
	Total		19 (100%)	9 (100%)	0 (0%)	0 (0%)

DISCUSSION

In our study, we encountered both Wormian and Inca bones variations more frequently in males. We observed Wormian bone most frequently in the lambdoid suture, similar to the results of different studies in the literature.

Wormian bones can be used to identify bone diseases such as scleidocranial dysostosis, pycnodysostosis, congenital hypothyroidism, and Ricket's or may serve as a marker in the identification of central nervous system anomaly diseases [16-20]. Wormian bone variation varies in different ethnic groups [18]. The Inca bone is one of the developmental skull variations. The incidence of Inca bones varies geographically. In a recent worldwide study, it was higher than 10% in Northwest coastal and West African people, while the Australian samples were outliers by Pacific standards with frequencies of 1% or less [9]. The prevalence studies of Wormian and Inca bones in different ethnic groups are given in Table 5 [21-26].

Table 5. Prevalence of Wormian bone and "Inca bone" in different populations

Studies	Population	Wormian bone prevalence (%)	Inca bone prevalence (%)	Maximum Incidence of Wormian bones with respect to sutures in skull
Cirpan et al. 2015 [21]	Western Anatolian	59.3%	6.7%	40.7% (*)
Sreekanth et al. 2016 [26]	Indian	53.15% (59/111)	8.10%	53.15% (*)
Ghosh et al. 2017 [22]	Eastern Indian	45% (54/120)	21.21%	53.33% (*)
Vijay et al. 2017 [24]	South Indian	61.5% (123/200)	23.57%	91.05% (*)
Natsis et al. 2019 [23]	Greek	74.7% (124/166)	-	44.6% (*)
Şafak et al. 2020 [25]	Turkish	42.86% (12/28)	9.37%	62.5% (*)
Present study	Central Anatolian	27.7% (33/119)	7.6%	57.6 (*)

*Lambdoid suture

In the studies in the Table 5, it is seen that the prevalence of Wormian bone varies in different geographical regions. In addition, we have seen that the incidence of Wormian bones may vary among people living in different parts of Anatolia (Table 5). We can interpret this situation as regional differences changing the frequency of Wormian bone variation. Despite the differences in the prevalence of Wormian bones, we saw that the region where these bones were most dense did not change (lambdoid suture). The second and next most common localization of Wormian bones varies according to studies [21-24].

Studies in which morphometric measurements were made for Inca and Wormian bones have been rarely encountered. One of these studies was conducted by Ogut and Yildirim, and Wormian bones were detected in 58 of 110 bones [27]. The sagittal diameter of these bones was 18.24±4.14 mm in females and 14.84±9.41 mm in male, the transverse diameter was 13.24±6.67 mm in females and 16.90±16.33 mm in males. In our study, morphometric measurements of Wormian bones localized in bregma and asterion were made. While the transverse diameter of these bones located in bregma was lower, the transverse diameter of the Wormian bones located in the asterion was similar to Ogut and Yildirim's [27]. Additionally, sagittal diameter measurements were found to be higher in the bones in our study.

In our study, it is detected Inca bones in 9 (7.6%) of 119 cranium. Table 5 shows the prevalence of Inca bone at different rates in different studies. Changes in the number of samples, genetic structure and geographical factors may have caused the differences in study results.

Studies looking at the sexual dimorphism of Wormian and Inca bones have found different results in different populations. In the study by Donapudi and Vijayanirmala, it was revealed that the incidence of both Wormian and Inca bone in male skulls was higher than that of females (male, 3.4%; female, 1.2%) [7]. In the study of Carolineberry and Berry, one of the epigenetic studies in the human cranium, it was reported that the Inca bone was detected at a rate of 4.6% in men and 2.9% in women [28]. These studies are also consistent with our results.

There are studies of metopic sutures and the incidence of Wormian bone accompanying this suture. Guerram et al. [29] 4.1%, Aksu et al. [30] 7.5%, Çalışkan et al. [31] 8.1% reported that they detected the rate of metopic suture in their study. In our study, we found metopic sutures in 13 of all bones (10.9%). We think that regional differences may cause this result. In one study, metopic sutures were detected in 29 of 285 Chinese heads. 26 of the skulls with metopic sutures are also reported to have Wormian bone [32]. We found that 8 of the 13 skulls we detected metopic suture had Wormian bones. Both studies support an increased likelihood of Wormian bone in craniums with metopic sutures.

Wu et al. [33] found with craniosynostosis in the presence of an Inca bone in 11 of 245 patients in total. They reported that the difference between the groups may be due to demographic or genetic differences. In our study, we did not detect cranial anomalies and Inca bone together. One of the 119 bones in our study had craniosynostosis. However, no additional bone was found in this bone.

O'Loughlin [34] showed that the incidence of Wormian bone increased in skulls with cranial deformation. In our study, no results compatible with these data were found.

During diagnostic or forensic identification, information on metopism, and craniosynostosis provides process-facilitating data. In addition, neurosurgeons should know Wormian bone in order not to harm during their interventions.

Limitations

The number of skulls used in the study was limited due to the removal of deformed ones.

CONCLUSIONS

We confirmed that the frequency of change in the skull of Wormian bones and Inca bones varies greatly. We concluded that Inca bones and Wormian bones are more common in males than females. In our study, we found Wormian bones (61.5%) in most of the 13 (10.9%) skulls with metopic suture. We found that the incidence of Wormian bone was increased in suture variations. In particular, clinicians need to be knowledgeable in order not to misinterpret suture bones as fractures. Therefore, we think that our study provides additional information to the literature on Wormian and Inca bones and will guide researchers dealing with sciences such as neurosurgery, radiology and anatomy in their practices.

Acknowledgments: The authors sincerely thank those who donated their bodies to science so that anatomical research could be performed.

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

Funding: The authors declared that this study has received no financial support.

Ethical Approval: This study was conducted on cadaver, it is among the studies that do not require ethics committee approval.
Informed Consent: The skulls used as educational materials

were obtained from Erciyes University Faculty of Medicine Anatomy Laboratory.

Author Contributions: Conception: H.G.- Design: H.G., H.K.G.E., B.K.A.- Supervision: H.G. -Materials: H.G., H.K.G.E. - Data Collection and/or Processing: H.K.G.E., B.K.A. - Analysis and/or Interpretation: H.G., H.K.G.E., B.K.A. - Literature Review: H.G., H.K.G.E. - Writing: H.G., H.K.G.E., B.K.A. - Critical Review: B.K.A.

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How to Cite;

Güler H, Güçlü Ekinci HK, Kamaşak Arpaçay B (2024) Variation of Wormian and Inca Bones in Adult Skulls. Eur J Ther. 30(3):332-339. https://doi.org/10.58600/eurjther1935

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):340-346.
https://doi.org/10.58600/eurjther1944

Original Research

An Investigation of the Knowledge and Preferences of Parents About Dental Preventive Practices

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Received: 2023-11-24 **Accepted:** 2024-02-25 **Published Online:** 2024-02-25

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ABSTRACT

Objective: Dental caries poses a significant health concern affecting, 60%-90% of children globally. While fluoride is widely utilized to prevent and eliminate dental caries, recent negative media coverage and concerns about irresponsible fluoride use have prompted a shift in parental perspectives. This study explores parental knowledge, preferences, and attitudes regarding preventive measures, with a focus on fluoride and potential natural or herbal alternatives.

Methods: Our research was designed as a survey study. A survey form consisting of 11 questions was delivered to parents of children aged 6–14 years and presented to the Erciyes University Department of Pediatric Dentistry for examination or treatment were included in the study. A total of 300 parents participated in the study. Data was recorded as numbers and percentages.

Results: Of the parents, 69% (207) reported that if they were offered natural herbal compounds instead of fluorinated varnish, they would prefer natural alternatives. A statistically significant relationship was found between the responses received from the parents about the effects of fluoride and the educational level of the parents ($p<0.05$). Only 4 (1.3%) university graduate parents stated that fluoride had harmful effects. We found that 80.95% of the fathers and 68.39% of the mothers stated that they would prefer natural or herbal alternatives for their children instead of fluorinated varnish, and this was a statistically significant result ($p<0.05$).

Conclusion: Parents do not have sufficient knowledge and attitudes about preventive practices in oral dental health, and some parents still avoid the use of fluoride products. Therefore, there is a need to increase fluoride intake and its effects on children's health by educating parents or informing dentists.

Keywords: Fluoride, Natural preparation, Pediatric dentistry

INTRODUCTION

Dental caries is an important health problem, affecting 60%-90% of children worldwide [1]. Caries can be eliminated and reversible in the early stages, but without appropriate care, it is not self-limiting and may progress until it completely destroys the tooth [2]. Fluoride, which is the most widely used protective material to prevent and eliminate dental caries, shows its caries-preventive effect on tooth enamel by preventing demineralization and increasing remineralization [3, 4]. Fluoride applications conducted professionally, such as fluoride gel, varnish, and

restorative materials, as well as fluoride-containing mouthwashes and toothpaste, are effective in reducing dental caries, which is a social health problem [5, 6]. Brushing the teeth twice a day with fluoridated toothpaste in the amount recommended by the dentist is effective in reducing caries. Fluoride applications administered by the dentist to people with high caries risk also prevent caries formation [7, 8]. In addition to the available information about the danger of irresponsible fluoride use at high doses, negative publicity about fluoride in print and visual media in recent years has changed parents' perspectives and preferences towards fluoride-containing products [9-11]. The vagueness regarding fluoride-related information has led to the idea that natural or herbal compounds can be used as an alternative to fluoride in preventing and eliminating dental caries [12]. There are several studies evaluating the perspective of parents regarding dental preventive practices in Turkey [9, 13-15]. However, previous studies have not investigated the opinions of parents regarding the use of natural/plant compounds with antiplaque properties, such as Centella asiatica, Echinacea purpurea, and Sambucus nigra, as alternatives to fluoride. Therefore, the aim of this study was to examine the knowledge level and preferences of parents with children aged 6-14 about preventive applications and to investigate their perspectives on alternative natural antimicrobials.

MATERIALS AND METHODS

Ethics committee approval for this study was obtained from the Erciyes University Non-Interventional Clinical Research Ethics Committee (Decision Date: 07.10.2020; Issue No: 96681246/ Decision No: 2020/494).

Parents of children aged 6–14 years who presented to the Erciyes University Department of Pediatric Dentistry for examination or treatment between 10.10.2020 and 30.12.2020 were included in the study. It was calculated that at least 284 participants should be evaluated according to power analysis (α=0.05, β=0.95) [9]. Considering the losses that may occur, 309 patients who presented to the Department of Pediatric Dentistry were evaluated. 9 surveys were excluded from the study because there were non-marked questions.

The questionnaire consisted of a total of 11 items. The first 3 items were about the sociodemographic characteristics (gender, age, education level, and income level) of the parent and the child; items 4-7 were about the parents' perspectives, behaviors/ attitudes, and knowledge levels about fluoridated products, and items 8-11 were about their attitudes towards fluoride applications and alternative natural products applied to children in the previous six months to one year (Table 1).

The questionnaires were filled out by the parents. Incomplete questionnaires were excluded from the study.

Table 1. Survey: Families' perspectives on fluoride

1. Mother's Age: Father's Age: Parent Mother/Father Child's Age:
2. Your monthly income a) Less than 2000 TL b) 2000-5000 TL c) 5000 TL or more
3. Your level of education: a) Primary school b) Secondary school c) High school d) University
4. What do you know about fluoride? a) I have no information. b) Prevents caries formation. c) Causes mental and developmental retardation d) Damages bones e) Good for teeth
5. Who would you prefer to administer fluoride-containing protective applications? a) Teacher b) Nurse c) Dentist d) Pedodontist e) No answer
6. Where do you get information about fluoride? a) Internet b) Pediatrician d) Dentist e) Neighbor f) Family
7. Would you prefer fluoride-containing toothpaste for your child? a) Yes b) No c) No answer
8. Is there a dentist who regularly follows your child? If yes, in which institution? a) Family health center b) Health center c) Private hospital d) Public hospital, clinic e) None

Main Points:

- In our study, it was determined that parents do not have sufficient knowledge and positive attitudes about preventive practices in oral dental health. Some parents avoid using fluoride products, which shows that education and awareness should be increased.
- In addition, it is thought that the fact that parents choose the natural preventive product when an alternative to fluoride is offered may guide studies on natural preventive products.

9. Has your child received a preventive fluoride treatment in the last six months? a) Yes b) No c) I don't know
10. Have you allowed your child to receive preventive fluoride gel applications at school? a) Yes b) No c) Our school did not conduct a preventive fluoride gel application
11. If you had the option of choosing a herbal or natural alternative to fluoride protective treatment, which one would you prefer? a) Fluoride varnish b) Herbal or Natural preparation

Statistical Analysis

The data obtained were analyzed with IBM Statistical Package for Social Science (SPSS) V23 (Armonk, NY: IBM Corp., USA). The Chi-Square and Fisher's exact tests were used to compare categorical variables according to groups. The results of the analysis are presented as mean ± standard deviation, median (minimum- maximum) for quantitative data, and frequency (percentage) for categorical data. The significance level was taken as $p<0.05$. The descriptive statistics of the responses are expressed as percentages.

RESULTS

A total of 300 parents, 174 females (58%) and 126 males (42%), participated in the study. The mean age of the parents was 36.8±5.27 years. Of the parents, 84 (28.8%) had a primary school education, 97 (32.3%) had a secondary school education, 80 (26.7%) had a high school education, and 39 (13.0%) had a university education (Table 2).

Table 2. Distribution of sociodemographic characteristics of the parents

	Frequency (n)	Percentage (%)
Parents		
Mother	174	58
Father	126	42
Parents' Education Level		
Primary School	84	28.0
Secondary School	97	32.3
High School	80	26.7
University	39	13.0
Parents' Income Level		
Low	75	25
Moderate	197	65.7
High	28	9.3
Total	300	100.0
Parents' Age	**Mean±SD**	**Min-max**
	36.8±5.27	27-51

(SD: standart deviation)

Of the parents, 20% (60) stated that fluoride prevents dental caries, 17% (51) stated that it is beneficial for teeth, and 58.3% (175) stated that they had no idea about fluoride.

If a fluoridated product is applied to their children, 159 (53%) parents stated that they would prefer the pedodontist's application, while 101 (33.7%) parents stated that they would prefer the dentist's application.

The sources from which parents obtained information about fluoride according to their level of education are given in Figure 1. Parents stated that they obtained information about fluoride mostly from dentists, and then from the internet or social media.

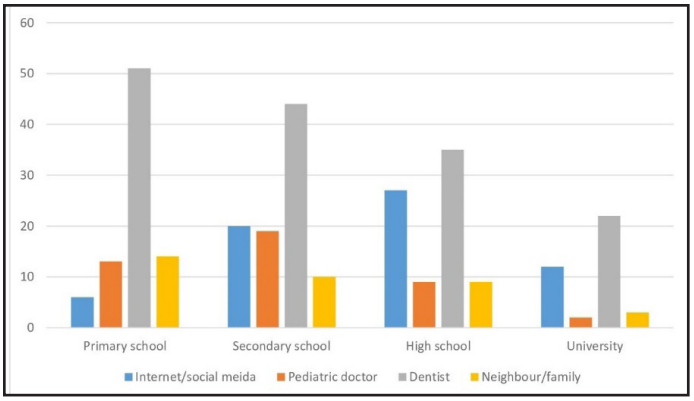

Figure 1. Parents' level of education and sources of information about fluoride

When asked whether they preferred toothpaste containing fluoride when choosing toothpaste for their children, 32.7% (98) parents stated that they preferred it, while 21.7% (65) parents stated that they did not.

Of the parents, 39.3% (118) reported that they regularly took their children to a dentist and they preferred state hospitals for these follow-up.

Of the parents, 28.3% (85) reported that their children had fluoride application in the last six months, while 55.3% (166) did not.

While 116 (39%) of the parents stated that they allowed their children to apply fluoride varnish at school, 37 (12%) stated that fluoride varnish was not applied at school (Figure 2).

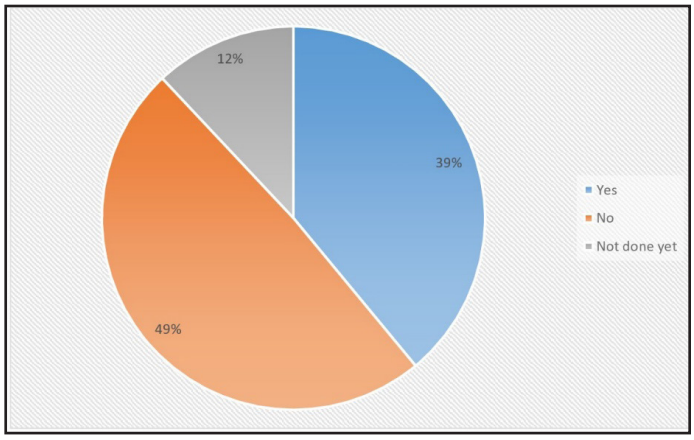

Figure 2. Percentage of parents who allow school-applied fluoride varnish

A statistically significant relationship was found between the responses received from the parents about the effects of fluoride and the educational level of the parents ($p<0.05$). Only 4 (1.3%) university graduate parents stated that fluoride had harmful effects. 41% of parents with a university education and 11.9% of the parents with a primary school education stated that fluoride application prevented caries formation.

There was no statistically significant relationship between the parents' preference for the person who would apply the fluoridated product and the level of education ($p>0.05$). Regardless of the level of education, the majority preferred a pedodontist.

It was found that the rate of choosing fluoridated toothpaste was higher among parents with high school and university education. While the rate of choosing fluoridated toothpaste among parents with high school and university education was 42.01%, this rate was 26.5% among parents with primary and secondary school education. A statistically significant relationship was found between parents' toothpaste preference for their children and education level ($p<0.05$) (Table 3).

Table 3. Parents' educational level and their opinions and preferences about fluoridated toothpaste

Education Level	Natural or Herbal Alternatives				Total
	Yes		No		
	n	(%)	n	(%)	p
Primary School	61	72.6	23	27.4	
Secondary School	55	56.7	42	44.3	
High School	62	77.5	18	22.5	**0.014**
University	29	74.4	10	25.6	
Total	207	69	93	31	300

Note: $p<0.05$, Chi-Square test

A statistically significant relationship was found between the parents' preference for natural orherbal alternatives instead of fluorinated varnish for their children and the level of education ($p<0.05$). There was no statistically significant relationship between parents' preference for natural or herbal alternatives instead of fluorinated varnish and income level. Of the parents, 69% (n=207) reported that they would prefer natural or herbal alternatives instead of fluorinated varnish.

We found that 80.95% of the fathers and 68.39% of the mothers stated that they would prefer natural or herbal alternatives for their children instead of fluorinated varnish and this was a statistically significant result ($p<0.05$).

DISCUSSION

Dental caries, one of the most common chronic infections in childhood, is a disease that results in disruption of the integrity of dental hard tissues [16, 17]. In studies conducted in Turkey, it is observed that the prevalence of caries in children aged 2-15 years ranges between 43.5% and 84.9% with an increasing trend [18, 19]. Accordingly, dental caries is still an important public health problem for children and their parents in Turkey. To decrease the prevalence of dental caries, which is a highly preventable disease, education and early diagnosis and preventive practices are of great importance [20]. Studies have shown that there are concerns in the society about the use of fluoride products [10, 21]. When the reasons for these concerns are analyzed, it is seen that they are mostly due to unsubstantiated information about fluoride on the social and print media [10].

Güler et al. [11] measured the level of knowledge of parents about fluoride in a study conducted with 50 parents. It was found that 48% of the participants allocated 1-3 hours a day to social

media tools, mostly (24%) obtained information about current issues from the internet (social media), and 35% found social media tools partially reliable. Similar results were obtained in our study. Of the parents, 21.7% reported that they received information about fluoride on the internet or social media.

Öter et al. [9] , in a study published in 2018, aimed to learn the knowledge levels and attitudes of parents with children aged 6-10 years about fluoride. They observed that parents did not have sufficient knowledge about fluoride applications and avoided the use of fluorinated products. In our study, we asked the parents "Did you allow your children to receive fluoridated varnish application during school screening?", and we found similar results. Of the parents, 49% reported that they did not allow for fluoridated varnish application at the school.

Çobanoğlu et al. [22] asked patients in different cities about their choice of fluoride in the toothpastes they used. While 13% of the patients used fluoride-free toothpaste, 40% reported that they thought fluoride-free toothpastes were more harmless. In addition, it was also found that patients did not deliberately choose toothpastes based on fluoride factor. The results obtained were found to be consistent with our study. In this study, it was found that 45.7% of the participants had no information about the choice of toothpaste for their children. Çobanoğlu et al. [22] reported that these results may be related to incomplete information provided by dentists to the parents. Since significant results ($p<0.05$) were obtained between the educational level of the parents and the choice of fluoridated toothpaste for their children in our study, we can say that the educational level of the parents is effective in the choice of fluoridated toothpaste in addition to incomplete information and inaccurate information disseminated by social media or TV.

Kalyoncu et al. [14] reported that 19 parents did not allow their children to receive topical fluoridated varnish application in public schools in their study titles "Attitudes and Approaches About Fluoride Varnish Application Program in Schools" conducted with parents in 2018, and of these 19 parents, 15.8% (n=3) reported that they were not sufficiently informed about the application, 26.3% (n=5) did not think that the application was performed in an appropriate environment, and 26.3% (n=5) thought that fluoride was harmful. Of the 40 parents who did not allow topical fluoride varnish application in a private school, 5% (n=2) reported that they were not adequately informed about the application, 22.5% (n=9) did not think that the application was performed in an appropriate environment, and 42.5% (n=17) thought that fluoride was harmful. Kalyoncu et al. [14] suggested that these results were due to insufficient knowledge of parents and that parents should be informed in detail about preventive applications, which have an important place within the scope of community oral and dental health promotion programs. In our study, we asked parents "What do you know about fluoride?" and found that 20% of the parents thought that fluoride varnish has various disadvantages (it causes mental and developmental retardation, damages bones, etc.). These results were found to be significantly correlated with parents' level of education. We think that educating parents can also help in solving this issue.

In studies published in the literature, parents' negative opinions about fluoride have led to the introduction of natural/herbal antimicrobial compounds as an alternative to fluoride [12, 23]. In the present study, we also asked the parents: "What would be your preference if a natural compound were to be used offered instead of fluoride varnish?", a statistically significant majority of parents (73.7%) preferred "natural/herbal alternatives".

Although fluoride has many advantages, different remineralization agents are being sought to replace the fluoride commonly used to provide remineralization. The reason for this is that excessive fluoride intake can be toxic. When taken regularly in small amounts, its toxicity can be acute or chronic, and in its chronic form, toxicity can affect mineralized tissues (bones and tooth enamel), leading to skeletal fluorosis and often dental fluorosis [24].

In recent years, great emphasis has been placed on research and education related to the identification of food components and the development of food products for health promotion. Numerous naturally occurring components in foods and vegetables have been shown to promote health and reduce the risk of many common diseases. It has been suggested that plant-derived antimicrobial compounds can be used as an alternative to the chemical compounds commonly used to control dental plaque and dental caries [12, 23]. In our study, although most of the parents stated that fluoride prevents dental caries and that they would prefer fluoridated toothpaste for their children, they reported that they would prefer natural/herbal alternatives instead of fluorinated varnish. This result suggests that when a natural-herbal product equivalent to fluoride is available in the future, parents may prefer these products more. We believe that this study will be beneficial in increasing the acceptability of

preventive measures in the community by exploring alternative natural compounds.

Limitations

The limitation of this study was that it is a cross-sectional study and was conducted in a single province in Turkey. In order to obtain generalizable results, a larger sample and studies in different regions should be conducted.

CONCLUSION

In conclusion, within the limitations of these studies, it is seen that parents do not have sufficient knowledge and attitudes about preventive practices in oral dental health, and some parents still avoid the use of fluoride products. Therefore, there is a need to increase fluoride intake and its effects on children's health by educating parents or informing dentists.

Conflict of interest: The authors have no conflicts of interest to declare.

Informed Consent: Received

Funding: There are no funding for this work.

Ethical Approval: Received, Decision Date: 07.10.2020; Issue No: 96681246/ Decision No: 2020/494

Author Contributions: Conception: Fatma Nur Kızılay and Esra Kızılcı -Design: Fatma Nur Kızılay and Türkan Mahyaddinova-Supervision: Esra Kızılcı -Fundings: none-Materials: Fatma Nur Kızılay -Data Collection and/or Processing: Türkan Mahyaddinova, Fatma Nur Kızılay -Analysis and/or Interpretation: Esra Kızılcı -Literature: Fatma Nur Kızılay and Türkan Mayhaddinova -Review: Esra Kızılcı -Writing: Fatma Nur Kızılay, Türkan Mahyaddinova, Zekiye Şeyma Gümüşboğa -Critical Review: Esra Kızılcı and Zekiye Şeyma Gümüşboğa.

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How to Cite;

Kızılay FN, Kızılcı E, Mahyaddinova T, Gümüşboğa ZŞ (2024) An Investigation of the Knowledge and Preferences of Parents About Dental Preventive Practices. Eur J Ther. 30(3):340-346. https://doi.org/10.58600/eurjther1944

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):347-353.
https://doi.org/10.58600/eurjther1948

Original Research

Does Being Treated for Osteoporosis Mean "Awareness"?

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Received: 2023-12-02 / **Accepted**: 2024-01-10 / **Published Online**: 2024-01-17

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ABSTRACT

Objective: Although there are studies evaluating Osteoporosis (OP) awareness in different populations, there is no study evaluating OP awareness in patients currently receiving medical treatment for OP in the Turkish population. The aim of this study was to evaluate the level of OP knowledge and associated factors in patients receiving medical treatment for OP.

Methods: 301 people diagnosed with OP and using OP medication for at least one year were included in the study. Demographic characteristics, risk factors associated with OP, duration of OP drug use were questioned. The 2011 Revised OP Knowledge Test (OKT) was applied to all participants.

Results: Of the 301 patients evaluated in the study, 274 (91%) were female and 27 (9%) were male. The mean age was 65.64 ±8.29. The patients had been using prescribed medication for 1 (1-20) years due to OP. Mean OKT-exercise score was 8.11±1.71, mean OKT-nutrition score was 9.04 ±1.99 and mean OKT-total score was 11.53±2.24. OKT-exercise, OKT-nutrition, and OKT-total scores were significantly positively correlated with educational status, income status, dietary calcium intake, protein intake, physical activity, and significantly negatively correlated with age. OKT-exercise sub-scores were significantly higher in those living in the city center.

Conclusion: It is seen that the level of knowledge of the patients is quite low, even if they have been using drugs for OP for years. This is a warning to physicians about whether adequate information is given about behavioral methods in addition to medical treatment.

Keywords: awareness, drug use, knowledge, osteoporosis

INTRODUCTION

Osteoporosis (OP) is a progressive bone disease that results in an increased risk of fractures [1]. More than 200 million women worldwide suffer from OP, resulting in 8.9 million fractures annually [2]. OP and its complications, especially hip fractures, cause physical, psychological, social, and economic burdens [2].

Despite the increased prevalence, increased mortality, and morbidity of OP, patients with OP are still under-diagnosed and under-treated [3]. Knowledge of bone health and active lifestyle are known as the main factors in keeping OP under control worldwide [4]. Many people unfamiliar with OP do not engage in regular osteoprotective behavior [5]. Therefore, adequate community screening and information should be provided to protect these patients.

In the literature, there are several studies investigating the information about OP in women in the geriatric age group, postmenopausal group, or those with a disease group that may lead to OP [6-12]. Although there are studies evaluating OP

awareness in different populations, there is no study evaluating OP awareness in patients currently receiving OP medical treatment in the Turkish population.

The aim of this study was to evaluate the level of OP knowledge and awareness and related factors in patients receiving OP medical treatment.

MATERIALS AND METHODS

Individuals aged 18 years and older, who had been taking OP medication for at least one year and who volunteered to participate in the study were included. Those who did not have sufficient mental capacity to answer the questionnaire and those who had been taking OP medication for less than one year were excluded. The age, gender, body mass index (BMI) education level, income level, marital status, comorbidity, drugs used, fracture history, parental history of hip fracture, smoking, alcohol and coffee consumption, and daily calcium intake, protein intake, and physical activity status were determined by face-to-face survey method. Those who did at least 3 days a week and at least 30 minutes of walking, cycling, and resistance exercise were considered to be at an adequate level of physical activity [13]. The OP drugs they used so far and their total duration of use were also noted.

The 2011 Revised OP Knowledge Test (OKT), which was validated and reliable in Turkish, was applied to all participants [14,15]. The 32-item OKT consists of two sub-scales related to nutrition and exercise, and these two sub-scales have 14 items in common. The correct answers are 1, wrong answers are scored as 0. The nutrition subscale ranges from 0 to 26 points, and the exercise sub-scale ranges between 0 and 20 points. The total score for OKT ranges from 0 to 32. According to this test, if the nutrition sub-score is 9.5 and above, the exercise sub-score is 9 and above, and the total score is 13 and above, it is considered sufficient [14,15]. In this study, the sample size was performed using the G * power (V3.1.7) program, at least 111 patients were found for total sample size with $\alpha = 0.05$, 95% power and d=0.3 effect size. The sample size was also compatible with similar previous studies [16-18].

This research has been approved by the Local Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

IBM SPSS statistical version 28.0 was used for statistical analysis. The suitability of the data to the normal distribution was evaluated by visual and analytical methods (Kolmogrov-Smirnov test). Categorical data were presented as n (%), non-normally distributed numeric data and ordinal data as median (minimum-maximum), and normally distributed numeric data as mean±standard deviation. In correlation analysis, Pearson correlation test was used for parametric data and Spearman correlation test was used for nonparametric data. Mann Whitney U test was used for comparison of two groups. A $p<0.05$ value was accepted for statistical significance.

RESULTS

Of the 301 patients evaluated in the study, 274 (91%) were female and 27 (9%) were male. The mean age was 65.64 ±8.29. Two hundred and fifty seven (85.4%) patients lived in the city center. Table 1 shows the demographic data of the patients.

The mean age of menopause was 46.75±5.6. Comorbid disease that may lead to OP (diabetes mellitus, rheumatic diseases, kidney or liver diseases, immunodeficiency, hypogonadism, hyperthyroidism, hyperparathyroidism, celiac disease, inflammatory bowel disease) in 105 (34.9%) patients was present. In 86 (28.6%) patients, there was drug use that could lead to OP (glucocorticoids, antiepileptics, proton pump inhibitors, thyroid hormone drugs, anticoagulants, immunosuppressives, antineoplastics). The patients had been using prescribed medication for 1 (1-20) years due to OP. Eighty two (27.2%) patients had fragility fractures. Table 2 shows the risk factors for OP.

Mean OKT-exercise score was 8.11±1.71, mean OKT-nutrition score was 9.04 ±1.99 and mean OKT-total score was 11.53±2.24 (OKT test results are listed in Table 3).

Main Points;

- The level of knowledge of the patients is quite low, even if they have been using drugs for OP for years.
- This is a warning to physicians about whether adequate information is given about behavioral methods in addition to medical treatment.

Table 1. Demographic Data of Patients (n=301)

Gender, n (%)	Woman	274 (91)
	Man	27 (9)
Age, mean (SD)	65.64±8.29	
BMI, mean (SD)	27.84±4.93	
Educational Status, n (%)	Illeterate	70 (23.3)
	0-5 years	105 (34.9)
	5-8 years	68 (22.6)
	8-12 years	47 (14.0)
	≥12 years	16 (5.3)
Marital Status, n (%)	Married	190 (63.1)
	Single	13 (4.3)
	Other	98 (32.6)
Income, n (%)	Good	156 (51.8)
	Low	145 (48.2)
Living Place, n (%)	City Center	257 (85.4)
	Village	44 (14.6)
OP Medication Duration, median (min-max)		1 (1-20)
OP Drugs Used so far, n (%)	Bisphosphonate	245 (81.4)
	Denosumab	25 (8.3)
	Bisphosphonate and Denosumab	29 (9.6)
	Bisphosphonate and Teriparatide	2 (0.7)

SD: Standard Deviation, BMI: Body Mass Index, OP: Osteoporosis

Table 2. Risk Factors for Osteoporosis

Age of menopause, mean (SD)		46.75±5.64
Fragility Fracture, n (%)	No	219 (72.8)
	Yes	82 (27.2)
Hip Fracture in Parents, n (%)	No	279 (92.7)
	Yes	22 (7.3)
Smoking, n (%)	No	264 (87.7)
	Yes	37 (12.3)
Alcohol Consumption, n (%)	No	284 (94.4)
	Yes	17 (5.6)
Dietary Calcium Intake*, n (%)	Inadequate	263 (87.4)
	Adequate	38 (12.6)
Daily Coffee Consumption, n (%)	<4 cups/day	272 (90.4)
	≥4 cups/day	29 (9.6)
Dietary Protein Intake, n (%)	<1 g/kg/day	257 (85.3)
	≥1 g/kg/day	44 (14.7)
Physical Activity, n (%)	Inadequate	286 (95)
	Adequate	15 (5.0)
Comorbidity that can lead to OP, n (%)	No	196 (65.1)
	Yes	105 (34.9)
Drug that can lead to OP, n (%)	No	215 (71.4)
	Yes	86 (28.6)

SD: Standard Deviation, OP: Osteoporosis, *The calculation system recommended by the International OP Foundation was used (http://www.iofbonehealth.org/calciumcalculator)

Tablo 3. Osteoporosis Knowledge Test Scores

	Mean (SD)
OK-exercise	8.11±1.71
OKT-nutrition	9.04±1.99
OKT-total	11.53±2.24

OKT: Osteoporosis Knowledge Test

Table 4 shows the results of the correlation analysis. OKT-exercise, OKT-nutrition, and OKT-total scores were statistically positively correlated with educational status (r/p=0.330/<0.001, 0.288/<0.001, and 0.450/<0.001 respectively), income status (r/p=0.140/0.015, 0.184/0.001, and 0.225/<0.001 respectively), dietary calcium intake (r/p=0.229/<0.001, 0.256/<0.001, and 0.191/<0.001 respectively), protein intake (r/p=0.277/<0.001, 0.244/<0.001, and 0.250/<0.001 respectively), physical activity (r/p=0.299/<0.001, 0.184/<0.001, and 0.284/<0.001 respectively), and statistically negatively correlated with age (r/p=-0.316/<0.001, -0.233/<0.001, and -0.434/<0.001 respectively). Only the correlations between OKT-total score and educational status and between OKT-total score and age were moderate, while the strength of all other correlations was weak.

OKT-exercise sub-scores were significantly higher in those living in the city center than in those living in rural areas (p=0.004), but there was no statistically significant difference in OKT-nutrition and OKT-total scores (p>0.05) (Table 5).

Table 4. Correlation Analysis Results

	OKT-exercise r/p	**OKT-nutrition r/p**	**OKT-total r/p**
Age	**-0.316/<0.001**	**-0.233/<0.001**	**-0.434/<0.001***
Educational Status	**0.330/<0.001**	**0.288/<0.001**	**0.450/<0.001****
Income	**0.140/0.015**	**0.184/0.001**	**0.225/<0.001****
Smoking	0.068/0.238	-0.015/ 0.791	0.102/0.078**
Alcohol Consumption	0.062/0.280	-0.012/0.833	0.048/0.453**
Coffee Consumption	0.163/0.005	0.048/0.403	0.178/0.002**
Dietary Calcium Intake	**0.229/<0.001**	**0.256/<0.001**	**0.191/<0.001****
Dietary Protein Intake	**0.277/<0.001**	**0.244/<0.001**	**0.250/<0.001****
Physical Activity	**0.299/<0.001**	**0.184/<0.001**	**0.284/<0.001****
OP Medication Duration	0.066/0.256	0.038/0.515	0.128/0.026**

*: Pearson Correlation Test, **: Spearman Correlation Test

Table 5. The relationship Between Osteoporosis Knowledge Level and Living Place, Drug Use, Comorbidities, Parental Hip Fracture, and Fracture History

		OKT-exercise		**OKT-nutrition**		**OKT-total**	
		Median (min-max)	**p***	**Median (min-max)**	**p***	**Median (min-max)**	**p***
Living Place	City Center	8 (4-15)	**0.004**	9(2-23)	0.175	12 (6-24)	0.119
	Village	7.5 (5-10)		8.5(5-12)		11 (8-16)	
Comorbidity that can lead to OP	Yes	8(4-15)	0.864	9 (2-15)	0.691	12 (6-16)	0.283
	No	8(4-15)		9 (4-23)		11(7-21)	
Frajility Fracture	Yes	8 (4-15)	0.417	9 (4-16)	0.919	11 (7-21)	0.312
	No	8 (4-15)		9 (2-23)		12 (6-18)	
Hip Fracture in Parents	Yes	8 (5-12)	0.322	9 (4-14)	0.955	12 (6-16)	0.520
	No	8 (4-15)		9 (2-23)		12 (7-21)	
Drug that can lead to OP	Yes	8 (4-15)	0.993	9 (2-13)	0.277	12 (7-16)	0.245
	No	8 (4-15)		9 (4-23)		11(6-21)	

*Mann Whitney U test

DISCUSSION

In our study, individuals who had been using an OP drug for at least one year were included and the OKT total score and sub-scores were found low. OKT-total score and sub-scores were found to be negatively correlated with age, positively correlated with educational and income status, dietary calcium and protein intake, and physical activity level. OKT-exercise sub-scores of those living in the city center were statistically significantly higher than those living in the village.

This study showed that the level of OP knowledge is low even in patients diagnosed and treated. In another study conducted in Brazil, in which the knowledge level of OP patients under antiresorptive treatment in the postmenopausal period was evaluated, the OPQ (OP questionnaire) was used to measure the knowledge level, and the OPQ score of the participants was low [16]. Although the scales used are different, these results are similar to ours. In another study comparing OP knowledge levels of premenopausal and postmenopausal women with and without OP, OKT results were found to be higher than our study [13]. In that study, it was also found that there was no statistically significant difference between the premenopausal and postmenopausal groups, and the knowledge levels of OP patients were similar to those without OP [13]. The differences in the number of patients and populations in the studies may have been effective in obtaining different results.

In our study, as in the studies of Altaş E et al.[18] and Kurt et al.[19], we found a decrease in the level of knowledge and awareness in advanced age. In another study measuring the knowledge level of the elderly living in rural areas, no significant correlation was found between age and knowledge level [20]. In this study we mentioned, only patients over the age of 65 were evaluated and a few survey questions were used instead of OKT [20]. In addition, those without a diagnosis of OP were also evaluated. These may be the reasons for the discrepancy between studies. Although awareness created at a young age prevents the development of OP as a result of preserving bone health, it is necessary to increase the knowledge level of the whole society in order to prevent complications in older ages [18].

In our study, similar to most of the literature, it was seen that education level and OP knowledge were positively correlated [13,21,22]. Better educated individuals may be more willing to learn about the OP or benefit from more written material in terms of access to information. On the other hand, there are a few studies that do not find a relationship between education level and OP knowledge level [23,24]. Differences in the mean age of the population in these studies may have contributed to the different results.

High income can increase the level of knowledge and awareness with various factors such as easy access to protein-rich foods. As in many studies, income and OP knowledge were positively correlated in our study. Surprisingly, there is a study in the literature showing that the level of OP knowledge decreases as the income level increases [25]. Differences in health policies or cultural differences in the residential areas where these studies were conducted may have led to different results. For example, the absence of significant public health education efforts on OP may be associated with such an outcome.

In our study, the OP knowledge level was also calculated to be significantly higher in those who took adequate calcium and protein and did adequate physical activity. This may be associated with higher income level. Perhaps, increased calcium and protein intake due to higher OP knowledge may also have had an impact on these results.

There are several studies that indicate that the level of OP knowledge is higher in urban areas than in rural areas [20,23,25]. Similarly, in our study, the OP-exercise score was significantly higher in those living in urban centers. This may be related to increased educational attainment in urban areas.

The first step in treating OP is to increase knowledge and awareness. To the best of our knowledge, this is the first study to examine the level of knowledge and related factors of individuals receiving OP treatment in the Turkish population. On the other hand, being a single-center and cross-sectional study is among the limitations of our study.

CONCLUSIONS

It is seen that the level of knowledge of the patients is quite low, even if they have been using drugs for OP for years. This is a warning to physicians about whether adequate information is given about behavioral methods in addition to medical treatment. Since OP is generally the problem of postmenopausal and advanced age, it is important to diversify the information methods with visual and auditory materials in a way that these age groups can understand.

Conflict of interest: All authors declare no conflict of interest.

Funding: No funding was received for this study.

Informed consent: The participants received oral and written information about the study and gave their written informed consent.

Ethics approval and consent to participate: The study protocol was approved by Health Sciences University Diskapi Yildirim Beyazit Education and Research Hospital Local Ethics Committee (04.07.2022, 141/05).

Authors' contributions: Z.K.U., D.C. and E.U.A. designed the study. Z.K.U., A.E.S.A., and M.K.S. collected the clinical data. Z.K.U., A.E.S.A., M.K.S. and D.C. analyzed and interpreted the patient data. All authors discussed the results, contributed to the final manuscript, and approved it. Z.K.U., D.C. and E.U.A. discussed the results and supervised all the research process. All authors approved the final manuscript and agreed to the published version of the manuscript.

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How to Cite;

Kirac Unal Z, Sen Akalin AE, Sezer MK, Cankurtaran D, Unlu Akyuz E (2024) Does Being Treated for Osteoporosis Mean "Awareness"?. Eur J Ther. 30(3):347-353. https://doi.org/10.58600/eurjther1948

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):354-361.
https://doi.org/10.58600/eurjther1976

Original Research

Evaluation of the Relationship Between Biomarkers and Disease Severity in Patients with Community-Acquired Pneumonia

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Received: 2023-12-22 / **Accepted**: 2024-01-25 / **Published Online:** 2024-01-29

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ABSTRACT

Objective: Biomarkers in community-acquired pneumonia (CAP) have the potential to facilitate clinical decisions by guiding the prediction of disease severity, treatment and prognosis. In this study, we evaluated the relationship of biomarkers with disease severity in patients with CAP.

Methods: 156 patients diagnosed with CAP were included in the study. Diagnosis of CAP was determined according to the Infectious Diseases Society of America (IDSA)/ American Thoracic Society(ATS) 2019 guidelines along with clinical findings. The CRB-65 scoring system was used to determine outpatient and hospitalized patients. Patient information was obtained retrospectively from their files. In these two patient groups; C-reactive protein (CRP), complete blood count (CBC) parameters, neutrophil/ lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/neutrophil ratio (MNR), lymphocyte/monocyte ratio (LMN), lymphocyte/CRP ratio (LCR), WBC/mean platelet volume ratio (WBC/MPV), CRP/MPV ratio, and MPV/PLT ratio were examined.

Results: Of the 156 patients included in the study, 72 were pneumonia patients receiving inpatient treatment (mean age 66.88±16.29) and 84 patients receiving outpatient treatment (mean age 51.57±16.68). Age was found to be statistically significant between the groups ($p< 0.001$). In the inpatient group; CRP, WBC, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, hematocrit, MPV, NLR, PLR, LMR, NMR, LMR, LCR, WBC/ MPV, and CRP/MPV were found to be significantly high ($p<0.05$). Parameters with diagnostic performance that may be helpful in distinguishing hospitalized patients with pneumonia are CRP/MPV (AUC:0.775, 95% CI:0.701-0.850), NLR (AUC:0.771, 95% CI:0.697-0.846) and CRP (AUC:0.758, 95% Cl:0.679-0.837).

Conclusion: NLR and CRP/MPV values, which can be measured easily and quickly together with CRP, can be used as additional tests to help distinguish patients with pneumonia requiring hospitalization.

Keywords: Biomarkers in Pneumonia, C-reactive protein, Community-acquired pneumonia, Disease Severity Assessment, Mean platelet volume

INTRODUCTION

Despite advancements in diagnostic and treatment methods, community-acquired pneumonia (CAP) continues to be a prevalent infectious disease that can lead to severe health issues and mortality [1,2]. In spite of precautions, the disease's effects and the burden on health systems are anticipated to increase in the upcoming years due to factors such as the nature of the disease and its rate of spread, the inadequacy of existing prevention strategies [3]. Clinical evaluation, pneumonia-specific severity scores, and biomarkers can provide additional information about the severity and etiology of the disease [4,5].

In CAP infections, it is important to determine the causative pathogens in disease management. However, identifying the causative pathogens is quite challenging and sometimes requires invasive methods. Non-invasive diagnostic methods that can identify outpatients and patients requiring hospitalization for CAP infections have been frequently investigated in recent years. Non-invasive diagnostic methods, such as identifying new specific biomarkers, can contribute to the evaluation and management of CAP. At the same time, they can identify CAP subgroups that require closer monitoring and determine patients who may have unfavorable long-term consequences [6–8].

Biomarkers are emerging as critical biological molecules in the evaluation of CAP. Acute phase proteins in the blood begin to increase in response to cytokines secreted by cells (tumor necrosis factor, interleukin-1, and 6). However, the appearance times of acute phase proteins are not specific. In particular, parameters such as WBC, neutrophils, CRP, and procalcitonin are known as inflammatory biomarkers in pneumonia [9,10]. They are assumed to be useful in assessing microbial features and the severity of illness in pneumonia, and in determining the course of antibiotic treatment [11–13].

Main Points:

- The role of biomarkers is important in determining the severity of the disease in patients with community-acquired pneumonia (CAP).
- Traditional biomarkers such as C-reactive protein and new biomarkers such as NLR and CRP/MPV play an important role in distinguishing pneumonia requiring hospitalization.
- The CRP/MPV ratio, as a simple and easily accessible biomarker, can guide the clinical decision-making process in determining the level of CAP.

Complete blood count (CBC) parameters are simple, inexpensive, and accessible measurements. There are studies suggesting that parameters such as red blood cell distribution width (RDW), MPV, and the ratios of CBC parameters (NLR, PLR, LMR, and MPV/PLT etc) are significant indicators of systemic inflammation [14,15]. Platelets play crucial roles in immune and inflammatory processes [16]. An increase in MPV is thought to be a sign of severe inflammation and elevated platelet activity [17]. In recent years, new parameters such as the CRP/MPV and WBC/MPV ratios have been studied to assess inflammation [9,18]. However, studies examining the significance of these ratios in the identification and monitoring of pneumonia and other diseases with acute inflammation are limited.

In this research, we assessed the values of CRP complete blood count parameters, and the biomarkers obtained by their ratios in determining disease severity and identifying patients requiring hospitalization in patients with CAP.

MATERIALS AND METHODS

The study was carried out by retrospectively reviewing the files of 2785 patients who presented to the Pulmonology Clinic of Konya Meram State Hospital between May 2022 and May 2023 and were diagnosed with pneumonia. Exclusion criteria for the study were set as patients under the age of 18, those who were PCR positive for Covid-19, and patients with missing or inaccessible laboratory and radiological data. Based on these criteria, 156 patients were included in the study. Laboratory parameters, radiological and demographic characteristics of the cases included in the study were obtained from the hospital information management system. The diagnosis of pneumonia was based on clinical findings as well as the guidelines of the American Infectious Diseases Society (IDSA)/American Thoracic Society (ATS) 2019. To decide on outpatient treatment or hospitalization, patients were divided into two groups using the CRB-65 scoring system (confusion, respiratory rate >30 breaths·min−1, blood pressure <90 mmHg (systolic) or <60 mmHg (diastolic), age >65 years). 72 patients (CRB-65=0) constituted the outpatient pneumonia group, and 84 patients (CRB-65≥1) constituted the inpatient pneumonia group. In addition, hospitalized patients were grouped within themselves according to their length of stay as 7 days and above and below 7 days. Case groups were evaluated by comparing them in terms of biomarkers and radiological findings. In both groups, complete blood count parameters such as CRP, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin-

Hbg, hematocrit-Htc, platelet-PLT, Platelet Distribution Width-PDW, plateletcrit-PCT, Mean Platelet Volume-MPV, and their ratios (Neutrophil/Lymphocyte ratio-NLR, Neutrophil/Monocyte ratio-LMR, Platelet/Lymphocyte ratio-PLR, Lymphocyte/CRP ratio-LCR, MPV/PLT ratio, and CRP/MPV ratio) were compared.

Statistical Analyses

The software SPSS 22.0 was used to analyze the data. The normal distribution was tested using the Kolmogorov-Smirnov method. For comparing continuous variables, the t-test or Mann-Whitney U test was recommended, while the chi-square test was utilized for categorical variables. The Pearson correlation test was used to look at the correlations between the variables. For diagnostic prediction and performance, ROC analysis and logistic regression were employed. The tests were deemed to have a significance level of $P<0.05$.

RESULTS

Of the 156 patients who met the admission criteria, 72 were treated as inpatients and 84 as outpatients. The average age were involved in the study as outpatients with pneumonia was 51.57 ± 16.68, while it was 66.88 ± 16.29 for those treated as inpatients. The average age of patients with pneumonia receiving treatment in the hospital was significantly higher compared to those treated as outpatients ($p< 0.001$). In the group of pneumonia patients treated in the hospital, CRP, WBC, neutrophils, lymphocytes, monocytes, basophils, hemoglobin, hematocrit, MPV, NLR, PLR, LMR, NMR, LCR, WBC/MPV ratio, and CRP/MPV ratio were considerably higher in comparison with the outpatient pneumonia group ($p< 0.05$) (Table 1).

Table 1. Comparison of Laboratory Parameters Between Patients Treated as Outpatients and Inpatients.

Parameters	Outpatient Pneumonia Cases (mean ± SD)	Inpatient Pneumonia Cases (mean ± SD)	p-value
AGE (years)	51.57±16.68	66.88±16.29	<0.001
WBC (/uL)	8.48±0.81	10.38±4.42	<0.001
Neutrophil (x10^3 /µL)	5.35±2.43	7.97±4.36	<0.001
Hbg (g/dL)	14.17±1.68	12.75±2.14	<0.001
Hct (%)	43.74±5.55	39.51±6.19	<0.001
MCV(fL)	86.76±6.05	88.10±5.66	0.158
PLT (x10^3 /µL)	259.97±72.91	271.79±80.288	0.337
PDW (fL)	19.17±2.35	19.02±2.33	0.684
MPV (fL)	8.54±1.44	7.94±1.40	0.010
PCT (ng/mL)	0.21±0.06	0.22±0.07	0.826
Lymphocyte (x10^3/µL)	2.21±0.78	1.57±0.73	0.001
Monocyte (x10^3 /µL)	0.63±0.23	0.66±0.28	0.007
Eosinophil (x10^3 /µL)	0.18±0.20	0.10±0.19	0.085
Basophil (x10^3 /µL	0.08±0.04	0.06±0.05	<0.001
CRP (mg/L)	12.75±14.08	51.18±49.47	<0.001
PLR	132.26±61.49	212.57±126.88	<0.001
NLR	2.72±1.66	6.41±5.2	<0.001
NMR	9.12±5.43	12.65±6.62	<0.001
LMR	3.86±1.76	2.78±1.83	<0.001
LCR	0.36±0.29	0.12±0.20	<0.001
WBC/MPV	1.02±0.40	1.33±0.60	<0.001
CRP/MPV	1.58±2.01	7.41±0.30	<0.001
MPV/PLT	0.03±0.01	0.03±0.01	0.100

WBC: White Blood Cells, Hbg: Hemoglobin, Hct: Hematocrit, MCV: Mean Corpuscular Volume, PLT: Platelets, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume, PCT: Plateletcrit, CRP: C-Reactive Protein, PLR: Platelet to Lymphocyte Ratio, NLR: Neutrophil to Lymphocyte Ratio, NMR: Neutrophil to Monocyte Ratio, LMR: Lymphocyte to Monocyte Ratio, LCR: Lymphocyte to CRP Ratio, WBC/MPV, CRP/MPV, MPV/PLT: Ratios of the respective parameters

No gender difference was observed between the patient groups (p> 0.05). Radiological findings showed substantial variations between the groups (p< 0.001). Bilateral multilobar involvement was more common in the group with pneumonia treated as inpatients, while minimal atypical involvement was more common in the group with pneumonia treated as outpatients (Table 2).

Correlation analysis revealed high levels of positive and negative relationships between laboratory values. The relationship between white blood cells (WBC) and neutrophils is quite strong (r 0.962, p< 0.01). Likewise, there is a strong positive correlations between WBC and the WBC/MPV ratio (r 0.912, p< 0.001). High levels of strong positive correlations were found between neutrophils and WBC (r 0.962, p< 0.001), neutrophils and the Neutrophil/Lymphocyte ratio (NLR) (r 0.749, p< 0.001), and neutrophils and WBC/MPV (r 0.885, p< 0.001). Additionally, strong positive correlations were found between CRP and CRP/MPV (r 0.783, p< 0.001), hemoglobin (Hbg) and hematocrit (Htc) (r 0.926, p<0.01), hemoglobin and red blood cell (RBC) (r 0.811, p<0.01), platelet (PLT) and MPV / PLT (r 0.782, p< 0.01). On the other hand, a strong negative correlation was determined between MPV/PLT and PLT (r 0.782, p< 0.01).

According to logistic regression analysis, factors predicting inpatient treatment of pneumonia patients were determined. Age factor (B: -0.039, Odds Ratio(OR): 0.961, 95% Confidence Interval (CI): 0.935-0.989, p=0.006), C-reactive protein (CRP) level (B: -0.048, OR: 0.954, CI: 0.933-0.975, p< 0.001), Neutrophil/Lymphocyte ratio(NLR) (B: -0.413, OR: 0.661, CI: 0.546-0.802, p< 0.001) and Mean Platelet Volume(MPV) (B: 0.462, OR: 1.587, CI: 1.108-2.274, p=0.012) were identified as s important components in predicting the necessity of hospitalization for pneumonia patients (Table 3).

Table 3. Predictive Factors for Patients Receiving Inpatient Treatment.

Parameters	B	OR	95%CI	p
Age	-0.039	0.961	0.935-0.989	0.006
CRP	-0.048	0.954	0.933-0.975	<0.001
NLR	-0.413	0.661	0.546-0.802	<0.001
MPV	0.462	1.587	1.108-2.274	0.012

B: Regression Coefficient, C-Reactive Protein (CRP), Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV), B values, Odds Ratios (OR), 95% Confidence Intervals (95% CI).

Table 2. Comparison of Gender and Radiological Findings Between Patients with Pneumonia Treated as Outpatients and Inpatients.

Parameters	Outpatient Pneumonia Patients n (%)	Inpatient Pneumonia Patients n (%)	p-value
GENDER			
Male	41 (48.8)	42 (58.3)	0.23
Female	43 (51.2)	30 (41.7)	
RADIOLOGY			
Minimal Atypical	54 (64.3)	0 (0.0)	
Unilateral Single Lobe	30 (35.7)	22 (30.6)	
Single Lung Multilober	0 (0.0)	16 (22.2)	<0.001*
Bilateral Multilober	0 (0.0)	34 (47.2)	

Chi-square Test. *Significant at the 0.05 level.

According to the results of the Receiver Operating Characteristic (ROC) analysis, it was observed that the diagnostic performances of CRP/MPV, NLR, and CRP values could be helpful in distinguishing pneumonia cases requiring hospital treatment from those that can be treated on an outpatient basis. The Area Under the Curve(AUC) and 95% confidence intervals(CI) are as follows: For CRP/MPV, AUC= 0.775 (95% CI: 0.701-0.850), for NLR, AUC=0.771 (95% CI: 0.697-0.846), and for CRP, AUC=0.758 (95% CI: 0.679-0.837) (Figure 1). The sensitivity and specificity values for the optimal threshold values of CRP/MPV, NLR, and CRP that can be used in diagnosis are as follows: For CRP/MPV, 1.26 (75.6% sensitivity and 60.0% specificity), for NLR, 2.48 (73.6% sensitivity and 58.3% specificity), and for CRP, 12.1 (73.6% sensitivity and 65.5% specificity) (Table 4).

Figure. ROC curves for the diagnostic performance of biomarkers in distinguishing pneumonia cases requiring hospital treatment.

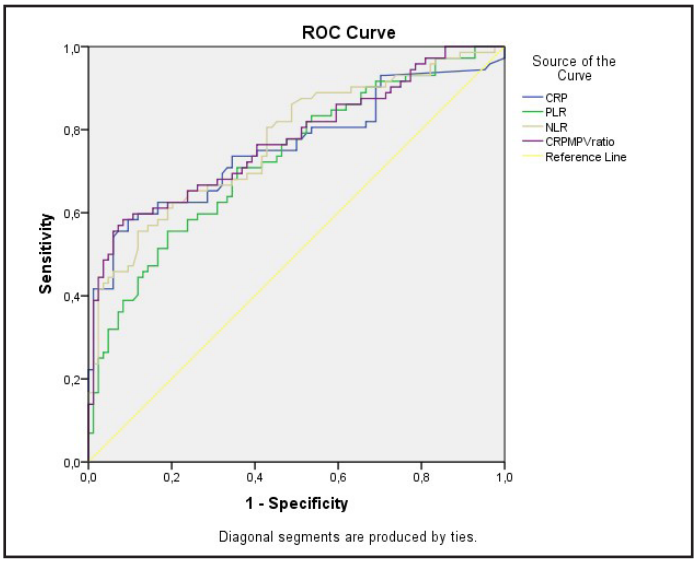

Table 4. Diagnostic Performance of CRP/MPV, NLR, and CRP Threshold Values in Predicting Hospitalized Pneumonia Patients According to ROC Analysis.

Parameters	Cutoff	Sensitivity, %	Specificity, %
CRP/MPV	1.26	75.6	60.0
NLR	2.48	73.6	58.3
CRP	12.1	73.6	65.5

C-Reactive Protein (CRP), Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV).

When patients with pneumonia were evaluated among themselves based on their length of stay, significant relationships were found between some biomarkers and length of stay. CRP, LCR, and CRP/MPV ratio were found substantially greater in patients staying in the hospital for 7 days and above ($p<0.05$) (Table 5).

Table 5. Relationship between Biomarkers and Length of Hospital Stay in Patients with Pneumonia Treated as Inpatients.

Parameters	Length of Hospital Stay <7 days Median (25%-75%)	Length of Hospital Stay ≥7 days Median (25%-75%)	p-value
AGE (years)	75.00 (47.00-79.00)	70.00 (61.25-78.00)	0.684
WBC (/uL)	7.80 (6.20-12.97)	9.30 (7.82-13.55)	0.382
Neutrophil (x103/µL)	5.50 (3.30-10.45)	6.45 (4.95-11.62)	0.364
Hgb (g/dL)	12.60 (10.55-13.95)	12.95 (11.50-14.57)	0.255
Hct (%)	38.80 (32.20-14.50)	40.24 (35.67-44.00)	0.187
MCV (fL)	86.60 (80.75-92.90)	88.35 (85.17-91.30)	0.390
PLT	252.00 (203.00-367.00)	281.00 (220.50-314.00)	0.855
PDW (fL)	19.30 (18.40-19.65)	19.55 (19.00-20.20)	0.145
MPV (fL)	7.40 (6.90-8.60)	7.90 (6.80-18.87)	0.472
PCT (ng/mL)	0.20 (0.10-0.30)	0.20 (0.20-0.30)	0.574
Lymphocyte (x103/µL)	1.40 (1.20-2.15)	1.45 (0.92-2.07)	0.621
Monocyte (x103 /µL)	0.70 (0.40-0.78)	0.70 (0.40-0.80)	0.962
Eosinophil (x103 /µL)	0.01 (0.00-0.15)	0.00 (0.00-0.10)	0.860
Basophil (x103 /µL)	0.10 (0.00-0.10)	0.10 (0.00-0.10)	0.467
CRP (mg/L)	8.54 (3.40-29.20)	48.70 (12.95-104.50)	0.002
RBC	4.40 (3.60-4.75)	4.50 (3.30-10.45)	0.325
PLR	191.66 (113.11-275.98)	192.66 (124.28-272.89)	0.645
NLR	3.43 (0.37-7.22)	4.87 (2.46-8.99)	0.310
NMR	11.00 (6.26-7.07)	11.68 (8.22-15.78)	0.440
LMR	2.55 (1.92-3.75)	2.14 (1.50-3.84)	0.420
LCR	0.18 (0.04-0.37)	0.63 (0.01-0.07)	0.001
WBC/MPV	1.00 (0.92-1.46)	1.14 (0.93-1.51)	0.393
CRP/MPV	1.00 (0.65-3.56)	7.45 (1.60-13.19)	0.001
MPV/PLT	0.03 (0.02-0.04)	0.03 (0.02-0.03)	0.978
Procalcitonin	0.05 (0.02-0.12)	0.05 (0.02-0.09)	0.375

WBC: White Blood Cells, Hbg: Hemoglobin, Hct: Hematocrit, MCV: Mean Corpuscular Volume, PLT: Platelets, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume, PCT: Plateletcrit, CRP: C-Reactive Protein, PLR: Platelet to Lymphocyte Ratio, NLR: Neutrophil to Lymphocyte Ratio, NMR: Neutrophil to Monocyte Ratio, LMR: Lymphocyte to Monocyte Ratio, LCR: Lymphocyte to CRP Ratio, WBC/MPV, CRP/MPV, MPV/PLT: Ratios of the respective parameters

DISCUSSION

This study has examined the function of biomarkers in assessing the necessity of hospital treatment in patients with CAP. The obtained results indicate that CRP, NLR, and CRP/MPV ratios are significant diagnostic biomarkers in patients with pneumonia who were treated in hospital. Parameters such as WBC, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, hematocrit, MPV, LMR, NMR, LMR, LCR, and WBC/MPV were observed to be notably elevated in hospital-treated pneumonia patients compared to those treated as outpatients.

Numerous studies have been reported on CBC parameters and biomarkers in patients with CAP [9,19,20]. While CRP and WBC are frequently used parameters, it is known that CRP and complete blood count parameters can be within normal values at the initial consultation of the patients. In addition, some blood values such as CRP may increase in bacterial infections while they may vary more in viral infections [9]. The fact that CRP and WBC are not specific inflammation biomarkers for CAP has led to studies on many new biomarkers and CBC parameters. In our study, unlike most studies, a number of CBC parameters and their ratios were studied together as biomarkers.

Complete blood count is used as an economical and practical tool in the evaluation of many diseases. In recent years, parameters such as NLR, LMR, PLR, and MPV/PLT based on CBC parameter ratios have been evaluated as bio-indicators of inflammation and their potential uses in community-acquired pneumonia are being investigated [21]. It has been reported in various studies that in systemic inflammation a**s** the number of neutrophils rises, the number of lymphocytes falls and platelets fulfill crucial roles in infection and inflammation [22,23]. It has been determined that platelets, beyond their hemostatic functions such as stopping bleeding, contribute to the accumulation of cells that cause inflammation to the damaged area by stimulating the emission of pro-inflammatory cytokines during inflammation. The decrease in platelet count during infection activates the bone marrow, resulting in the production of young platelets with a wider diameter compared to mature platelets. This situation leads to an increase in MPV values. Studies have revealed that an increase in MPV could be considered as an indicator of illness-related inflammation such as rheumatoid arthritis, cystic fibrosis, and pneumonia [22,24,25]. We observed no significant differences in PLT, and plateletcrit (PCT) values between our pneumonia patient groups.

Recently, biomarkers such as WBC/MPV and CRP/MPV, which use the ratios of traditional acute phase proteins to MPV, have come to the fore in many studies. In particular, they are thought to be new prognostic markers in showing the relationship between inflammation and atherosclerosis in cardiovascular disease risk classification [18,26]. In our study, we determined that WBC/MPV and CRP/MPV ratios were markedly greater in patients with pneumonia requiring hospitalization. These findings indicate that in cases of pneumonia, WBC and CRP levels rise, and the ratios obtained by dividing these values by MPV also increase. This situation may be a useful method in assessing the intensity of the illness. It is critical to determine if a patient with community-acquired pneumonia will receive inpatient or outpatient care. This can be done by accurately assessing the intensity of the illness at the beginning. Depending on the severity of the disease; antimicrobial therapy, the route and length of administration, as well as microbiological investigations vary.

In our study, CRP/MPV, NLR, CRP, and MPV were the prominent parameters in diagnostic adequacy and prediction analyses in pneumonia patients. Among these parameters, the diagnostic performance of CRP/MPV in hospitalized pneumonia cases was found to be higher than the others. The rapid availability of these inflammatory indicators can enable the effective identification of patients requiring hospitalization in pneumonia cases. This provides an opportunity for early and accurate treatment, reducing morbidity and mortality. Based on the data we obtained from our study, we believe that CRP/MPV, in addition to CRP, NLR, and MPV, and especially CRP/MPV as a new marker, will guide clinicians in assessing the level of CAP. In addition, we observed a relationship between the duration of hospitalization and certain biomarkers. The CRP, LCR, and CRP/MPV ratios of patients with a longer than seven-day hospital stay were statistically higher than those with a stay of less than 7 days.

Limitations

There were limitations in our study, such as its retrospective nature and the exclusion of comorbid diseases from the data analysis.

CONCLUSIONS

In conclusion, it is known that traditional inflammatory markers employed in determining the treatment method in pneumonia developed in the community do not always provide precise and clear results. This study demonstrates that, along with standard tests such as CRP and WBC, recent biomarkers such as CRP/

MPV and NLR may also be useful in determining the severity of the disease. In health institutions with limited facilities, these parameters can be used quickly and effectively to determine the indication for hospitalization. However, we believe that more comprehensive investigations are needed to determine the definitive correlation between community-acquired pneumonia and biomarkers.

Financial Conflict of Interest: There is no financial conflict of interest in the study.

Conflict of Interest: There is no conflict of interest in the study.

Funding: No funding was obtained for this study.

Ethics Committee: The study commenced after obtaining approval from the KTO Karatay University Faculty of Medicine Non-Drug and Non-Medical Device Research Ethics Committee on the date of 25.05.2023 with the approval number 2023/019.

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How to Cite;

Yeşildağ M, Özkan Bakdık B, Balasar B, Eroğlu E (2024) Evaluation of the Relationship Between Biomarkers and Disease Severity in Patients with Community-Acquired Pneumonia. Eur J Ther. 30(3):354-361. https://doi.org/10.58600/eurjther1976

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):362-367.
https://doi.org/10.58600/eurjther2038

Letter to Editor

Left Bundle Branch Optimized Implantable Cardioverter Defibrillator (LOT-ICD) Implantation in a Patient with Myotonic Dystrophy

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Received: 2024-01-30 **Accepted**: 2024-02-25 **Published Online**: 2024-02-29

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Abstract

Left bundle branch (LBB) optimized implantable cardioverter defibrillator (LOT-ICD) is a recently emerged alternative to the standard biventricular pacing - ICD (BiVp-ICD). The IS-1 connector pin of the ICD lead was closed with a protective cap and the LBB pacing (LBBP) lead was inserted into the ICD generator at the ventricular P/S hole. Herein, we presented a myotonic dystrophy patient who underwent LOT-ICD device implantation because of a high degree of atrioventricular block and heart failure with mid-range ejection fraction. A DDD-ICD (DF-1) was implanted in our patient which has been attached to the atrial lead (RA hole), the LBBP lead (ventricular IS-1 hole), and the ICD lead (ventricular DF-1 hole). The IS-1 pin of the ICD lead was closed accordingly. The LOT-ICD should be considered an option to standard BiVp-ICD associated with lower cost, lower procedure time, and no phrenic nerve capture.

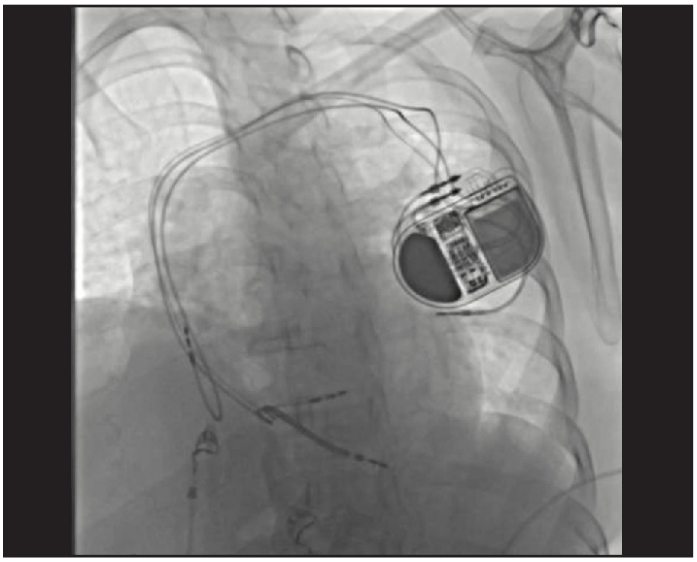
Keywords: Implantable cardioverter defibrillator, left bundle branch pacing

Letter to Editor,

Patients with myotonic dystrophy type 1 (MD1) have an increased risk of sudden cardiac death because of cardiac involvement and conduction abnormalities [1, 2]. Permanent pacemaker implantation is recommended in MD1 patients with advanced atrioventricular block (AVB) independent of the symptoms [3]. Cardiac resynchronization therapy (CRT) may be considered in DM1 patients who have permanent pacemaker dependency and left ventricular ejection fraction (LVEF) of <50% [4]. Although overt myocardial involvement in DM1 is infrequent, CRT implantation in DM1 patients was also reported previously [5-7].

Left bundle branch pacing (LBBP) is emerged as an alternative pacing method to biventricular CRT [8, 9]. The LBBP is achieved by inserting an electrode into the interventricular septum [10]. Several recent studies implicated that, LBBP is a more effective method and could be an alternative to biventricular CRT [11, 12]. Furthermore, in a recent research, another novel method was emerged and implemented as LBB optimized implantable cardioverter defibrillator (LOT-ICD) due to its high cost of biventricular CRT-D (IS-1 pin of the ventricular lead was closed with a protective cap and LBBP electrode was inserted into ventricular-P/S hole of ICD generator). This method had a lower cost and showed stable lead parameters. Herein, we presented a myotonic dystrophy patient with heart failure with mid-range ejection fraction (HFmrEF) and advanced atrioventricular block (AVB) in whom the LOT-ICD method was used.

A written and verbal informed consent was taken from the patient for submission of this paper. We did not use artificial intelligence (AI)– assisted technologies in the production of submitted work. A 51-year-old female patient with the diagnosis of MD1 and HFmrEF has been hospitalized for a rehabilitation program and consulted us for symptomatic bradycardia (dizziness and pre-syncope). She was under treatment of metoprolol 50 mg/day, Ramipril 2,5 mg/day, and spironolactone 25 mg/day for HFmrEF. She had no known history of coronary artery disease and her coronary angiography which was performed 7 years ago was normal. Cardiac magnetic resonance imaging (MRI) at the time of HFmrEF revealed no septal scar and LVEF of 41%. Her electrocardiography (ECG) showed sinus rhythm (40 bpm) and a trifascicular block (right bundle branch block, alternating left anterior/posterior hemi block, and first-degree AV block with PR interval of 400 ms) (Figure 1A). Furthermore, another ECG showed a second-degree Mobitz type 2 AVB and ventricular rate of 35 bpm (Figure 1B). Laboratory tests were unremarkable. Transthoracic echocardiography revealed an LVEF of 43% and moderate mitral and tricuspid regurgitation. Metoprolol treatment was stopped. As the patient was symptomatic, a temporary transvenous pacemaker was implanted to bridge the waiting period for metoprolol clearance (Figure 2). However, no improvement in the patient's rhythm was observed, and recurrent non-sustained ventricular tachycardia (NSVT) episodes were documented on telemetry recordings. As the patient would be pacemaker dependent and the LVEF was between 36-50%, we planned to implant a dual-chamber LOT-ICD device functioning as a CRT-D. Under local anesthesia and sedation, a left axillary vein puncture was performed. DF-1 ICD lead was placed into the right ventricle apex. Then, Solia S60 ventricular lead was inserted deep into the mid-interventricular septum with the support of Selectra 3D 55-39 (Biotronik, Berlin, Germany) delivery sheath and unipolar pacing parameters were compatible with the non-selective LBBP (V6 R wave peak time of 72 ms and V6-V1 inter-peak delay 40 ms, and a QRS transition during threshold test) (Supplementary Video 1). Pacing parameters of unipolar and bipolar pacing threshold/impedances were 0.6 and 0.7 V @ 0.4 ms / 615 and 773 ohms, R wave sense amplitude: 8.6 mV. Thereafter, atrial lead was placed into the right atrial appendage. After slitting the delivery sheath and fixation of the leads to the muscular tissue with the sleeves, the atrial lead pin was inserted into the RA hole, the defibrillation lead pin was inserted into the ventricular DF-1 hole, and the LBBP lead was inserted into the ventricular IS-1 port of the DDD-ICD (DF-1) pulse generator. IS-1 pin of the ventricular lead was closed with a protective cap and had left freely (Figure 3A & B). Post-procedural ECG showed a paced QRS duration of 120 ms with bipolar pacing of the device (Figure 4). No periprocedural complication was observed and the remaining hospitalization was uneventful. Beta-blocker treatment was re-initiated accordingly. The patient was asymptomatic and the pacemaker parameters were normal in the 1st and 3rd follow-up visits.



Supplementary Video 1. Contrast injection via delivery sheath showed the depth of the left bundle branch pacing lead in the septum. (Available at https://eurjther.com/index.php/home/article/view/2038/1546)

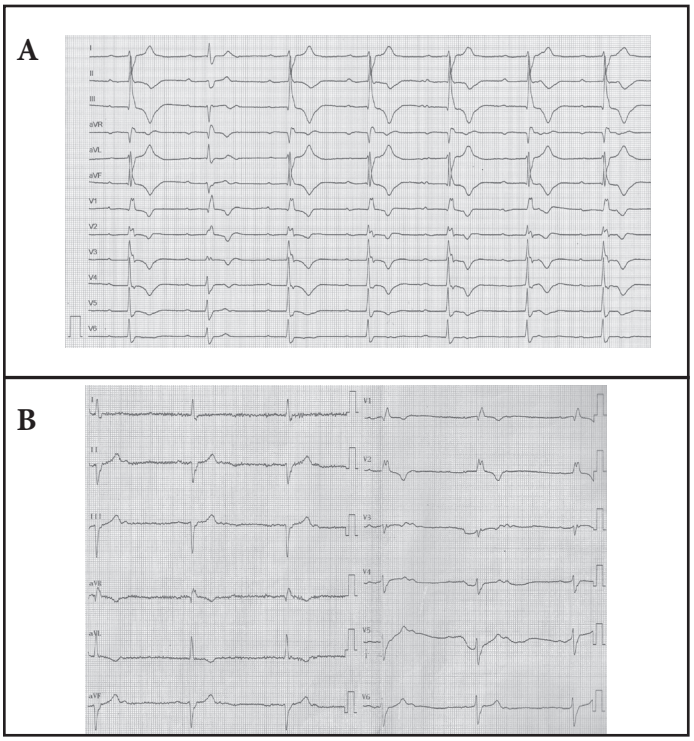


Figure 1. A. Electrocardiography showed sinus rhythm (40 bpm) and a trifascicular block (right bundle branch block, alternating left anterior/posterior hemi-block, and first-degree AV block with PR interval of 400 ms). **B.** Follow-up electrocardiography showed a second-degree Mobitz type 2 AV block and ventricular rate of 35 bpm.

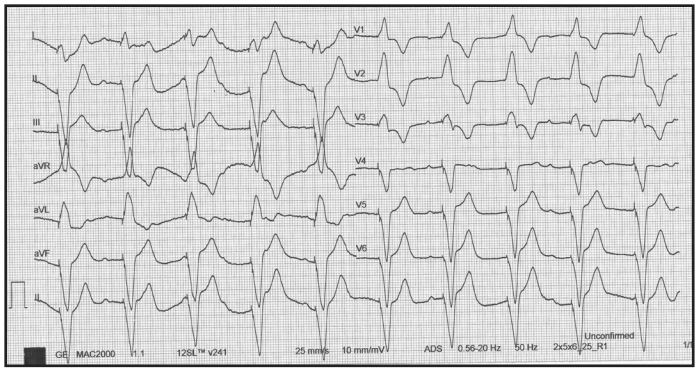


Figure 2. Electrocardiography showed a pacemaker rhythm with a paced QRS duration of 200 ms

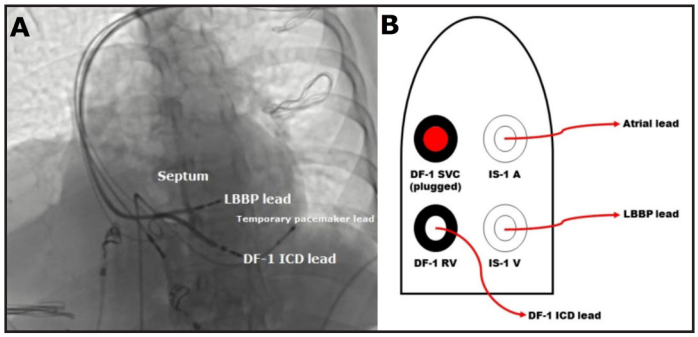


Figure 3. A. The fluoroscopy at the left anterior oblique view shows the localizations of the LOT-ICD device leads. **B.** The connections of the LOT-ICD device lead to the pulse generator.

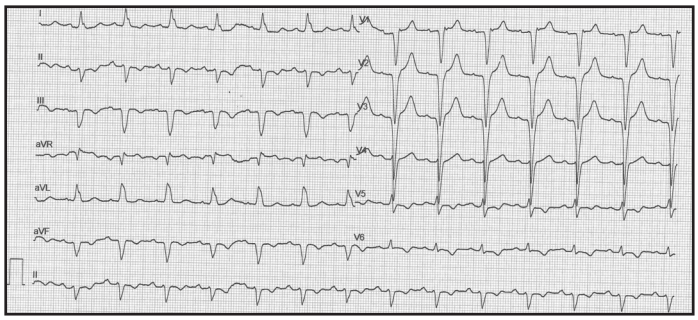


Figure 4. Post-procedural electrocardiography showed a paced QRS duration of 120 ms with bipolar pacing of the LOT-ICD device and terminal small r wave in V1 derivation.

In the current paper, we presented a female patient with MD1 and HFmrEF who consulted us for symptomatic bradycardia in whom a dual-chamber LOT-ICD device was implanted. MD1 is an autosomal dominant neuromuscular disorder characterized by multi-systemic involvement including the heart. It has been reported that sudden cardiac death can occur in MD1 patients because of myocardial and conduction system involvement [1, 2]. Overt myocardial involvement was rarely reported [5-7]. Although there were various data about conduction system abnormalities and permanent pacemaker implantation [1, 3], the data about biventricular CRT implantation in MD1 patients was scarce [5-7]. Furthermore, there is no clear consensus about biventricular CRT or ICD implantation in MD1. Groh et al. [1] reported the presence of atrial tachyarrhythmia, a PR interval > 240 milliseconds, aberrant QRS conduction, and advanced AV block as significant predictors of sudden death. In a recent study, Benhayon et al. [13] showed that the presence of AV conduction abnormalities in MD1 patients was also associated with an increased risk for ventricular tachyarrhythmia. Their study also revealed that one-third of the MD patients who received a primary prevention ICD experienced ventricular arrhythmia during a 22-month follow-up. Thus, it has been suggested that there is a role for CRT-ICD in DM1 patients who require permanent pacemaker implantation based on the progressive nature of the cardiac involvement [14]. Following the previous literature, our patient experienced multiple NSVT episodes with the risk factors for ventricular tachyarrhythmia and sudden cardiac death such as an advanced AV block, aberrant QRS conduction, and mid-range myocardial involvement. Thus, we implanted a pacemaker with a defibrillator function.

LBBP has emerged and is adopted very fast in clinical practice [10]. It has better LV synchronization and acute hemodynamic response compared to biventricular CRT [15]. Recent studies showed that CRT via LBBP was more effective than biventricular CRT [11, 12]. Interventricular septal scar and severe His-Purkinje conduction abnormality were prognostic factors for ineffective LBBP alone, and cMRI-guided LBBP might be a better option to be successful [16, 17]. LOT-CRT or HOT-CRT are better options in case of extensive septal scar or severe His-Purkinje conduction abnormality. LOT-ICD is a recently emerged cost-effective resynchronization technique. DDD-ICD generator ventricular P/S hole is occupied by LBBP lead, and the IS-1 pin of ICD lead is closed with a protective cap. It is shown that the LOT-ICD is associated with stable R wave sensing in arrhythmia detection, low cost, and low procedure time that cause lower radiation dose.

Furthermore, the LOT-ICD resulted in significant improvement of LVEF, LV end-diastolic diameter, and QRS durations of the patients [18]. It also overcomes the limitations of biventricular CRT implantation such as coronary sinus lead dislodgement, absence of appropriate coronary sinus branch, non-response to biventricular CRT, and phrenic nerve capture [19]. The main reason for using a LOT-ICD device rather than a biventricular CRT device is its lower cost of the pulse generator. Ponnusamy et al. [18] reported a 30% reduction in the cost of the therapy without any obstacle in clinical response with the LOT-ICD device. This novel cost-effective resynchronization method can be preferred in developing or under-developed countries with limited health sources and no reimbursement for device therapies [20]. Our MD1 patient had a symptomatic advanced AV block, documented NSVT episodes, and HFmrEF (LVEF 43%). It is recommended to perform a cardiac physiological pacing (LBBP or His bundle pacing) or biventricular CRT in such a patient who requires substantial ventricular pacing, NSVT episodes, and LVEF of 36-50%. The presence of myocardial involvement and an advanced AV block were thought as significant risk factors for sudden death in our patient. Thus, we prefer to perform LOT-ICD functioning as a CRT-D.

In conclusion, LOT-ICD is a promising alternative to biventricular CRT-D that has lower cost and mostly better pacing and procedure-related properties. Future large-scale randomized studies comparing LOT-ICD with biventricular BiVp-ICD are needed.

Funding: None.

Conflict of interest: U.C.: Proctoring for Biotronik & Medtronic; S.C.K. and M.D.: None declared.

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How to Cite;

Kara SC, Dogan M, Canpolat U (2024) Left Bundle Branch Optimized Implantable Cardioverter Defibrillator (LOT-ICD) Implantation in a Patient with Myotonic Dystrophy. Eur J Ther. 30(3):362-367. https://doi.org/10.58600/eurjther2038

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):368-371.
https://doi.org/10.58600/eurjther2076

Letter to Editor

The Clock is Ticking: Overcoming Time with Mechanical Thrombectomy for Middle Cerebral Artery Infarct

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Received: 2024-03-03 **Accepted**: 2024-05-02 **Published Online**: 2024-05-14

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Abstract

Coronary angiography is associated with several documented complications, and cardioembolic stroke following angiography is a rare occurrence. This letter to editor presents a case involving thrombotic occlusion of the left middle cerebral artery (MCA) during coronary angiography. A 36-year-old female patient, presenting to the emergency department with chest pain, underwent coronary angiography due to non-ST-segment elevation myocardial infarction. While the responsible lesion underwent revascularization, the patient experienced new-onset motor deficits and aphasia. DSA imaging was conducted on the patient, whose diffusion magnetic resonance imaging and clinical findings were indicative of MCA infarction. Thrombectomy was performed on the patient with a left MCA infarction. Proficient management of neurological complications underscores the potential positive impact of interventional treatment strategies on mortality and morbidity. In this letter to the editor, the significance of early diagnosis, appropriate treatment, and multidisciplinary approach is emphasized.

Keywords: Interventional cardiology, middle cerebral artery infarction, mca infarction, cardioembolic stroke, thrombectomy

Dear Editor,

Coronary angiography (CAG) is associated with various complications, with clinically significant incidents occurring at a frequency of 0.3-1%. Patient groups susceptible to complications encompass those with a history of female gender, advanced age, atherosclerosis, anticoagulant drug use, obesity, and hypertension. Complications not only extend patients' hospitalization periods but also contribute to elevated morbidity and mortality rates. While prevalent complications include bleeding, femoral artery pseudoaneurysm, hematoma, arteriovenous fistula, deep vein thrombosis (DVT), and thromboembolism, neurological complications are encountered infrequently [1]. This article presents a case involving thrombotic occlusion of the left middle cerebral artery (MCA) during CAG.

Patient Information

A 36-year-old female patient with a medical history of diabetes, hypertension, and ten years of hemodialysis utilizing an arteriovenous fistula was admitted to the emergency department with a diagnosis of non-ST elevation myocardial infarction. Upon admission, her blood pressure measured 145/80 mmHg,

and the electrocardiogram showed sinus rhythm, t-negativity in the inferior leads, and 1 mm ST depression. The ejection fraction was determined to be 40%. Angiography was performed via the right femoral route, revealing a plaque in the left system. An 80% thrombosed lesion was identified in the mid-RCA region, classified as an acute lesion. The patient received 7000 IU of unfractionated heparin, followed by the implantation of a 3.5*40 mm drug-eluting stent (DES) into the RCA after predilatation with a 2.75*20 mm balloon. During the procedure, our patient manifested drowsiness and neurological deficits. In the neurological examination, a slight blurring of the right nasolabial sulcus, muscle strength of 2-3/5 on the right side, the left arm overcoming gravity with painful stimulation, the left lower extremity being able to pull, and the right-side showing Babinski positivity and aphasia were observed. The patient underwent cranial imaging, and diffusion magnetic resonance (MR) imaging revealed an infarct in the left middle cerebral artery (MCA) area (Fig. 1). Given the concordance between physical examination findings and diffusion MRI results indicative of MCA infarction, digital subtraction angiography (DSA) imaging was performed to assess potential thromboembolic complications. Thrombectomy was performed on the patient with a high HAS-BLEED score, whose left middle cerebral artery (MCA) was observed to be occluded on digital subtraction angiography (DSA) images (Figs. 2 and 3). In the control DSA images taken after the procedure, it was observed that the MCA flow was successfully restored (Fig. 2). During the follow-up after thrombectomy, the patient regained consciousness, and their neurological examination improved, leading to discharge with full recovery.

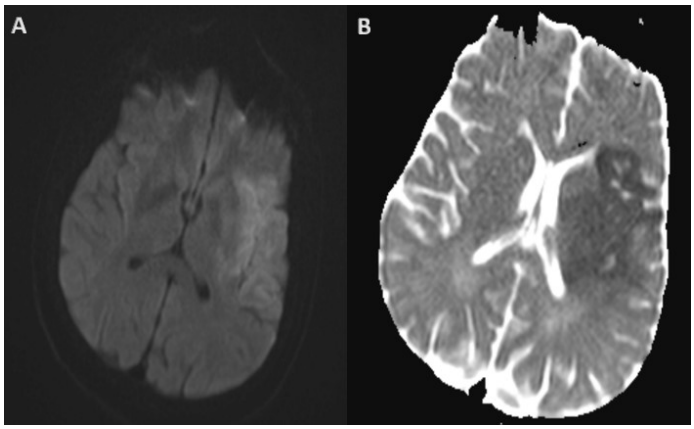

Figure 1. Appearance of infarction in the left Middle Cerebral Artery (MCA) area on diffusion MRI

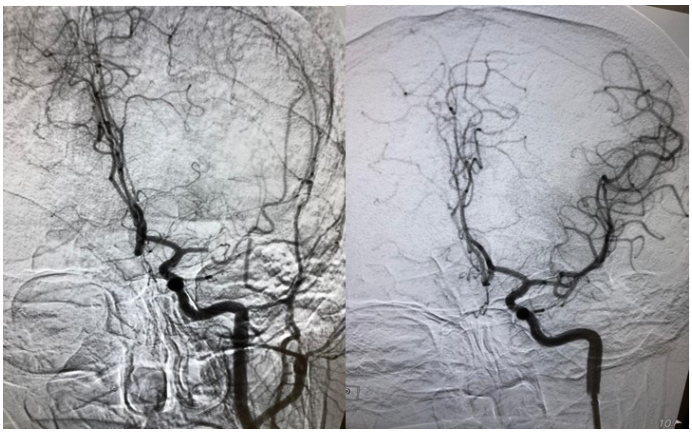

Figure 2.A. DSA image prior to thrombectomy, and **B:** DSA image post-thrombectomy

Figure 3. Material obtained through thrombus aspiration.

Discussion and Conclusion

Coronary artery disease (CAD) stands as the most prevalent cardiovascular ailment. Despite encountering fewer adverse outcomes with the increased prevalence of CAD and the advancements and heightened experience in interventional and medical treatments in this domain, complications persist as an inherent aspect of our practice. In addition to more commonplace complications such as bleeding, pseudoaneurysm, arrhythmias, coronary artery dissection, allergic reactions to contrast material, and acute renal failure, neurological complications, including contrast-related encephalopathy [2] and cardioembolic stroke, are observed rarely. Valve diseases, particularly atrial fibrillation, ischemic cardiovascular diseases, heart failure,

patent foramen ovale, and infective endocarditis, constitute the etiological factors for ischemic stroke, with iatrogenic stroke being an additional cause. Approximately 85% of strokes arise from ischemic origins, and of these, around one-fourth are attributed to cardioembolic causes [3]. The involvement of different vascular regions in cranial imaging serves as a potential indicator of cardioembolic stroke, with the left middle cerebral artery being a commonly affected site [4]. Similarly, in our case, diffusion MRI images reveal infarction consistent with the left middle cerebral artery (MCA) area, supporting the diagnosis of cardioembolic stroke. Instances of left MCA infarction secondary to infective endocarditis [5] and left ventricle thrombus [6] have been documented in the literature. Mirroring the progress in interventional treatments for cardiovascular diseases, significant advancements have occurred in the field of endovascular intervention, complementing thrombolytic approaches. For these patients, mechanical thrombectomy serves as a treatment option, offering an alternative to thrombolytic therapy, particularly in cases associated with a heightened risk of bleeding [7-9]. The proficient management of neurological complications underscores the potential positive impact of interventional treatment strategies on mortality and morbidity. This case report underscores the significance of early diagnosis, suitable treatment, and a multidisciplinary approach.

Yours sincerely,

Funding: This study received no funding.

Conflict of Interest: The authors report no conflict of interest. Each author takes responsibility for all aspects of their liability and freedom from bias of the data presented and their discussed interpretation.

Ethical Statement: The authors stated that ethics committee approval was not required for this letter to editor and written informed consent was obtained from the patient.

Acknowledgement: The authors declare that no support from AI-based assistive technologies was received in the preparation of this paper.

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How to Cite;

Aydın N, Sertdemir AL (2024) The Clock is Ticking: Overcoming Time with Mechanical Thrombectomy for Middle Cerebral Artery Infarct. Eur J Ther. 30(3):368-371. https://doi.org/10.58600/eurjther2076

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):372-373.
https://doi.org/10.58600/eurjther2083

Letter to Editor

A Rare Complication of the Parastomal Hernia: Extensive Colonic Ischemia

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Received: 2024-03-10 **Accepted**: 2024-04-25 **Published Online**: 2024-05-06

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Dear Editor,

Parastomal hernia (PH) is a condition caused by migration of abdominal viscera or tissue into the fascial defect around the stoma. The probability of PH after ostomy can be seen up to 65%. Although the ostomy increases patient survival, it may also increase postoperative complications. Incarceration or strangulation of the small and large intestine in the hernia is rarely seen [1,2]. We present an elderly female patient with extensive colonic necrosis due to strangulation in PH.

An 88-year-old female patient was admitted to the emergency department with complaints of diffuse abdominal pain and nausea for two days. The patient's medical history revealed that she underwent abdominoperineal resection (miles) and a permanent end colostomy for anorectal cancer 20 years ago. The patient had congestive heart disease and hypertension. The patient was also obese (body weight index: 30). Physical examination revealed a laparotomy scar in the midline of the abdomen and a colostomy in the left side of the abdomen. In addition, a 30x25 cm PH was detected around the colostomy. Abdominal palpation detected diffuse abdominal tenderness and rebound. White blood cell count was 13.500/mm^3 and C-reactive protein was 6.5 mg/L. Biochemical parameters were within normal values. Computed tomography showed that the hepatic flexura, transverse colon, splenic flexura, descending colon, and sigmoid colon segments were in PH (Figure 1a). The patient was operated under emergency conditions because of acute abdomen. All colon segments were ischemic and necrosed until the middle of the ascending colon (Figure 1b).

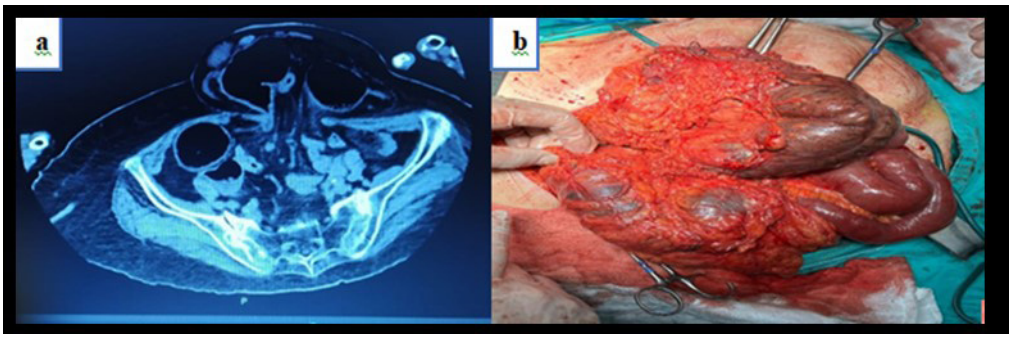

Figure 1.a. Strangulated colonic segments in parastomal hernia in computed tomography, **b.** Necrotic colonic segments

In addition, since a 1x2 cm polyp was detected in the cecum, total colectomy and end ileostomy were performed. During postoperative intensive care unit follow-up, the patient's general condition deteriorated and the patient died one day after the operation.

Parastomal hernia was observed up to 28% in patients with ileostomy and 48% in patients with end colostomy [3,4]. Patient-related risk factors for PH are advanced age, female gender, obesity, systemic infection, smoking, collagen disorder, obstructive uropathy, diabetes mellitus, constipation, chronic obstructive pulmonary disease, and presence of colostomy for more than 10 years. The factors related to the surgical technique for PH are inappropriate stoma selection, stoma being larger than 2.5 cm, excessive separation and tension in the rectus abdominal muscle, epigastric nerve denervation, and emergency stoma forming [4]. The patient presented had a lot of risk factors for PH such as advanced age, female gender, obesity, and presence of end colostomy for 20 years. Although there are no guidelines for the management of ostomy-related PH, this complication can be treated surgically or non-surgically. Weight loss in obese patients may help to improve the symptoms of PH. The surgical method used in PH varies depending on the patient's hemodynamic status and organ necrosis/ischemia. It was stated in literature that early treatment of PH with tension-free mesh reduces the rate of late complications [5]. PH should be repaired with tension-free mesh in early stage to avoid serious complications.

Sincerely,

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How to Cite;

Taşkın Aİ. (2024) A Rare Complication of the Parastomal Hernia: Extensive Colonic Ischa. Eur J Ther. 30(3):372-373. https://doi.org/10.58600/eurjther2083

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):374-376.
https://doi.org/10.58600/eurjther2109

Letter to Editor

Is It Really True that Artificial Intelligence does not have the Potential to be an Author?

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Received: 2024-03-24 **Accepted**: 2024-04-25 **Published Online**: 2024-04-27

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Dear Editors,

Artificial intelligence (AI) technologies have become a global priority due to their recent surge in popularity. This rapid development arouses excitement in some people and creates anxiety in others. The latest developments, which dramatically affect all areas of social life and business, are closely followed by the scientific community.

I have been following with interest the recent important discussions on artificial intelligence tools in your journal. Scientists are debating whether AI can be the author of a scientific paper.

The International Committee of Medical Journal Editors (ICMJE), an organization with international credibility, recommends the following four basic criteria for becoming an author [1].

"Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND Drafting the work or reviewing it critically for important intellectual content; AND Final approval of the version to be published; AND 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."

ICMJE also opened a special section on artificial intelligence-assisted technologies (AI-ATs) and recommended the following in summary.

"Authors should indicate that the article uses AI (such as Large Language Models [LLMs], chatbots, or image creators). If the AI-AT is used as a writing assistant, it should be described in the acknowledgement section; if it is used to collect and analyze data and generate figures, it should be described in the material method section. Since AI-ATs may provide incorrect or biased information, the final check should be carried out by a human author and the responsibility for the article should belong to him/her. Therefore, AI-ATs should not be listed

as an author and AI should not be cited" [1].

Does AI-AT meet ICMJE author criteria? What if it does?
Recently, AI-ATs are often used as a tool for editing the article or for performing some analysis. In such a use, it would be sufficient to mention that AI-ATs were used in the material-method or acknowledgement section. But AI-ATs are also capable of identifying the problem, providing solutions for the identified problem, analyzing and synthesizing the results. It is obvious that these capabilities of AI-ATs will be further developed in the near future. This kind of use will make AI-ATs meet the author requirements recommended by ICMJE.

On the other hand, it is quite common for AI-ATs to provide inaccurate, biased or low-reliability information. Debates about this are still ongoing in the literature [2]. However, although article publishing processes are completed within the framework of certain rules and controls, these erroneous behaviors are sometimes encountered in human authors. As of right now, no research has been done to compare the information content of articles produced by humans and those written by AI-ATs in terms of bias or error. The lack of data makes it impossible to conclude that AI-ATs are more biased or mistake-prone than human authors, and vice versa.

Responsibility for written products lies with the author, as stated by ICMJE. According to the copyright rules in force, the author must be a human being [2, 3]. It is a fact that AI-ATs cannot be held responsible for an error and no sanctions can be imposed on them. There are also studies in the literature that suggest that support from AI-ATs can be utilized but the final check should be done by a human author [4]. Furthermore, it's unclear which publications AI-ATs were able to access and if they were granted official authorization to do so. A lawsuit over this matter is currently pending, brought by multiple authors against OpenAI [5].

At this point, it is important to mention the AI-ATs that are already evolving day by day and designed specifically for scientific papers. We cannot blame an AI-AT for its writing, its hypothesis, the incorrect or biased information it conveys. But if AI companies launch a product developed specifically for academic writing and take responsibility for any mistakes it may make, then concerns about responsibility can be eliminated.

As a result, AI technology is progressing so fast that what is valid and accurate when you first read this article may be invalid or inadequate the next time you read it. AI is rapidly developing and changing day by day, and its potential is unpredictable. Therefore, making binding decisions and/or setting rules on AI for the future involves some risks. I think it would be better to take such a sector step by step with short-term rules and to establish a definite rule template after the final point (if any) that AI will eventually reach is determined. In other words, nowadays AI is more of an accelerator or facilitator than a play maker in articles. In this context, it would be appropriate to talk about AI-ATs, which are used in the material method section, as other supporting academic tools. But if we wake up one morning and AI comes to our screen with a research proposal, if it can present the planning and budgeting of the research, the potential contributions of the research to science, the risk points and their solutions, the concept of authorship may need to be completely redesigned.

Regards,

Acknowledgements: The study text was written with the help of artificial intelligence assisted technologies.

Declaration of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding Statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Deveci A. (2024) Is It Really True that Artificial Intelligence does not have the Potential to be an Author?. Eur J Ther. 30(3):374-376. https://doi.org/10.58600/eurjther2109

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):377-381.
https://doi.org/10.58600/eurjther2111

Letter to Editor

Corticosteroids and Immunosuppressants on Oral Lichen Planus' Treatment

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Received: 2024-03-25 **Accepted**: 2024-05-10 **Published Online**: 2024-05-14

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Dear Editor,

Lichen planus (LP), a chronic inflammatory condition primarily targeting skin and mucous membranes, was first outlined by Wilson in 1869 and histologically by Dubreuilh in 1906 [1]. It predominantly affects women in their 4th and 5th decades [2]. Oral lichen planus (OLP) occurs mainly on the buccal mucosa, gingiva, and tongue, presenting in six types, with erosive ones causing eating discomfort. While 25% of LP cases manifest solely orally, some lesions can appear in areas like the anogenital region and esophagus [2].

OLP is postulated to be a T cell-mediated response to antigens, with potential ties to chronic liver diseases and higher prevalence in regions like Japan and Southern Europe [3]. Comorbidities like diabetes, hypertension, and stress may also contribute [4]. Dental materials can mimic OLP, and specific drugs, including NSAIDs and beta-blockers, might induce it in some individuals [5].

Asymptomatic OLP lesions generally need no treatment. For symptomatic forms, treatment targets symptom alleviation and lesion removal, primarily using topical corticosteroids. Resistant lesions may require intralesional or systemic corticosteroids, with alternatives like immunosuppressives, retinoids, antifungals, and metronidazole also being effective [6].

OLP has a premalignant nature with a 0.4-1.74% risk of turning malignant, typically from its atrophic or erosive form [7]. Treatment aims to alleviate pain, heal ulcers, minimize cancer risks, extend symptom-free periods, and uphold oral health. This report presents intralesional corticosteroid therapy for three patients with symptomatic OLP, presenting symptoms like pain and burning.

The diagnosis, treatment and follow-up processes of the patients diagnosed with oral lichen planus in the three patients are described in detail in Table 1.

Table 1. The diagnostic, treatment, and follow-up processes of patients diagnosed with lichen planus

Patients	Anamnesis, and Patient Complaint	Diagnosis	Treatment Plan	Follow-up
1st	• 27-year-old • Male • Non-smoker • Without systemic disease ***Complaints*** - Severe pain in the right buccal mucosa, - Increased salivation, - Inability to eat of patient, - Lesions occurred frequently.	***Examination*** - Intraorally, an erosive lesion covering the right buccal mucosa was detected with a white periphery and erythema in the middle (**Fig. 1a**). ***Diagnose*** - Incisional biopsy was performed. - As a result of the pathological and clinical examinations, OLP without any epithelial dysplasia was diagnosed.	- An intralesional corticosteroid ***(0.5 mL dose of triamcinolone acetonide; 40 mg/mL; Kenacort, Han All Bio-Pharma)*** administration was applied - On the control session after 20 days, observed that the lesion regressed, and the complaints of patient decreased (**Fig. 1b**). - A second dose of corticosteroid was administered to ensure complete recovery.	- The patient was called back for control 1 week later. The patient did not come to the control session because he had completely healed the intraoral lesions, and during the 2-year follow-up period, he did not apply to our clinic with any complaints.
2nd	• 48-year-old • Male, • Non-smoker, • Without systemic disease ***Complaints*** - Pain, - Tenderness in the oral mucosa, - Increased burning sensation while eating spicy food.	***Intraoral examination*** - white-lined erythematous areas in the anterior gingiva and buccal sulcus (**Fig. 2a**). ***Diagnose*** - In the anamnesis, it was determined that a biopsy was performed in the dermatology department and a diagnosis of lichen planus was made.	- Patient used local orticosteroids and applied them to herbal treatment, when diagnosed by dermatologist. However, he stated that he could not get results from the treatments and that his complaints increased in some periods. - Intralesional corticosteroid injection ***(0.5 mL dose of triamcinolone acetonide; 40 mg/mL; Kenacort, Han All Bio-Pharma)*** injection was performed to relieve the patient's complaints (**Fig. 2b**). - The patient was also given a pomade containing ***orafix-clobetasol propionate (0.05%)*** and asked to apply it four times a day. - Periodontal treatment of the patient, whose oral hygiene was not good, was performed. - The fixed prosthesis in the lower anterior was renewed.	- In the control session, it was determined that the patient's complaints decreased, and the lesions regressed after 3 weeks. (**Fig. 3**).
3rd	• 59-year-old, • Female • Non-smoking patient • With asthma, type 2 diabetes, polyneuropathy, irritable bowel syndrome, and cholesterol diseases ***Complaints*** - Severe pain and sensitivity to hot and spicy foods.	***Intraoral examination*** - Hyperkeratotic lines, - Erosive and hyperemic areas were observed in the buccal mucosa and gingiva (**Fig. 4a**). ***Diagnose*** - It was found that the patient had previously applied to dermatology with the same complaints and was diagnosed with lichen planus 3 years ago.	- In the anamnesis, it was detected that the patient was treated with systemic corticosteroids, but the patient did not use her medications regularly, because of the side effects of systemic corticostreoids on her bowels. - Periodontal treatment was planned for the patient with poor oral hygiene. - ***Tacrolin 0.1% pomade (Farma-Tek, Sakarya, Türkiye)*** was prescribed to the patient on alternate days, 4x1 and 2x1 in intermediate doses, and she was followed up. Despite decreasing the complaints after using Tacrolin pomade (0.1 %, Farma-Tek, Sakarya, Türkiye) (**Fig. 4b**), the patient had limited time to stay in Türkiye. - Considering her complaints and limited time, we decided to treat the lesions with intralesional corticosteroids ***(0.5 mL dose of triamcinolone acetonide; 40 mg/mL; Kenacort, Han All Bio-Pharma).*** Intralesional corticosteroid therapy was applied to the patient 2 times with an interval of 2 weeks.	- It was observed that the lesions of the patient regressed, the mucosa returned to normal, and her complaints decreased after 2 weeks (**Fig. 5,6**).

First patient is a 27-year-old non-smoking male exhibited an erosive buccal lesion with associated pain and eating difficulties (Fig. 1a). His history noted recurrent lesions. Biopsy confirmed OLP without epithelial dysplasia. An intralesional triamcinolone acetonide injection was administered due to severe pain. Notable lesion improvement was observed at a 20-day review (Fig. 1b). Despite a secondary corticosteroid administration, the patient self-reported full recovery and had no recurrence over a 2-year period.

Second patient is a 48-year-old non-smoking male presented with oral discomfort and sensitivity to spicy foods. Examination revealed erythematous regions in the anterior gingiva and buccal sulcus suggestive of lichen planus (Fig. 2a), previously confirmed by biopsy. Despite earlier treatments, symptoms persisted. We administered an intralesional triamcinolone acetonide injection (Fig. 2b) and prescribed orafix-clobetasol propionate (0.05%) pomade. Combined with dental interventions, a three-week review showed reduced symptoms and lesion improvement (Fig. 3).

And third patient is a 59-year-old non-smoking female with multiple health conditions presented with severe oral pain and sensitivity. Previously diagnosed with lichen planus, she had sporadic systemic corticosteroid use due to side effects. After limited relief from Tacrolin 0.1% pomade, she underwent two sessions of intralesional corticosteroid treatment with triamcinolone acetonide. This led to significant symptom relief and lesion regression within two weeks.

In conclusion, therapeutic intervention is typically reserved for symptomatic patients for OLP. Advised lifestyle adjustments encompass tobacco reduction, limited alcohol consumption, and the avoidance of irritant foods. Symptomatic patients, presenting with discomforts like pain or burning, require prompt symptom alleviation, attainable through therapeutic avenues such as corticosteroid administration, both local and systemic, or advanced surgical and laser techniques.

Yours sincerely

Figure 1.a. Intraoral view presenting with the complaint of pain in the buccal mucosa, **b.** Buccal mucosa image of the patient who was called for control 20 days after intralesional corticosteroid injection.

Figure 2.a. Intraoral view of the patient who came to our clinic with the complaint of burning in the gums and buccal sulcus. **b.** Intralesional corticosteroid application

Figure 3. Intraoral view of the patient of control session after 3 weeks of injection

Figure 4.a. Hyperkeratotic lines, erosive and hyperemic areas on the buccal mucosa and gingiva in intraoral examination, **b.** Image of the buccal mucosa after the use of Tacrolin 0.1% pomade

Figure 5. Intraoral view of the patient after 2 weeks for follow-up examination

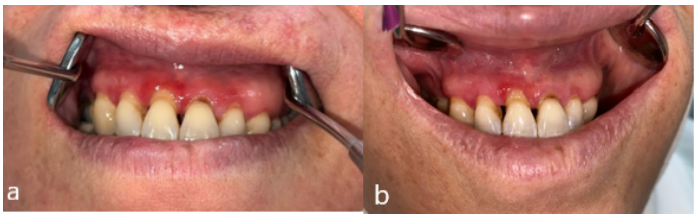

Figure 6. Intraoral view of maxillary anterior region before treatment (a) and after application of intralesional corticostereoids (b).

Acknowledgments: None declared.

Conflict of interest: None declared.

Funding: None declared.

Ethical Approval: Not applicable, but we have patients' consent statements.

Informed Consent: There are patient consent statements and they can be shared with the editor if necessary.

Author Contributions: Conception: MA; SU - Design: MA; SU; AA; GM - Supervision: AA; GM; KO - Fundings: MA; SU; AA; GM -Materials: MA; SU - Data Collection and/or Processing: MA; SU - Analysis and/or Interpretation: MA; SU; AA; GM; KO - Literature: MA; SU; AA; GM - Review: MA; SU; AA; GM - Writing: MA; SU; AA; GM - Critical Review: AA; GM;KO

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How to Cite;

Akyüz M, Uzun S, Altindağ A, Mağat G, Orhan K (2024) Corticosteroids and Immunosuppressants on Oral Lichen Planus' Treatment. Eur J Ther. 30(3):377-381. https://doi.org/10.58600/eurjther2111

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):382-385.
https://doi.org/10.58600/eurjther2116

Letter to Editor

Multifocal Osteonecrosis in Spinal Cord Injury

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Received: 2024-03-27 **Accepted**: 2024-05-12 **Published Online**: 2024-05-14

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Dear Editors,

Necrosis of the bone marrow and trabecular portion as a result of limited blood flow is known as osteonecrosis (ON) [1]. Several causes have been proposed for the development of ON, including vascular occlusions, ischemia, intravascular coagulation in interosseous tissue, increased intracortical pressure, mechanical stress, precursor cell death, and suppression of angiogenesis. There are multiple risk factors and medical condition associated with ON, including infections, hematological and coagulation problems, connective tissue illnesses, kidney diseases, excessive alcohol and tobacco use, and the use of corticosteroids and cytotoxic drugs [2].

Multifocal osteonecrosis, defined as the presence of osteonecrosis in three or more bone sites, is a rare entity representing less than 3% of osteonecrosis patients [3].

Due to its potent anti-inflammatory properties, methyl prednisolone (MP), one of the most extensively used corticosteroids, has been used for a long time in the acute phase of spinal cord injury and brain edema due to its strong anti-inflammatory properties [4]. Although studies have reported cases of multifocal osteonecrosis (MFON) brought on by corticosteroid medication, this link has never been examined in a patient with a spinal cord injury.

This letter aims to highlight MFON that occurred in a patient who underwent acute spinal cord injury and high-dose steroid therapy.

Patient Information

A 24-year-old man who underwent general surgery in another facility owing to hepatic and intestinal damage as a result of a gunshot wound was monitored in the anesthetic intensive care unit of our hospital for 11 days. He had no prior history of smoking, alcohol usage, or any other diseases. After being followed up in the intensive care unit for 2 weeks, the patient was started to be followed up in the neurosurgery service with undisplaced fractures posterior to T11-12 vertebral bodies and paraplegia clinic and patient was not operated. He received steroid treatment, which was started during his intensive care stay and continued while he was

hospitalized in the neurosurgery ward, four intravenous doses of 40 mg of steroids totaling 2880 mg over the course of 18 days. Enoxaparin was started on the 4th day of her hospitalization in the intensive care unit. The patient was transferred to our clinic in August with a diagnosis of T11(ASIA-A) paraplegia in order to receive rehabilitation.

The patient with flaccid paralysis had edema in both knees, an elevated body temperature, and a passive restriction of 40 degrees in flexion. ALP levels in the serum were measured in lab testing to be 224 IU/L (30-120), Calcium levels was 10.1 mg/dL (8.8-10.6), and Phosphor levels was 5.0 mg/d (2.5-4.5) respectively. The CRP was above the normal range at 2.7 (0-0.5) and the erythrocyte sedimentation rate was 81 mm/hr.

These observations led to the tentative diagnosis of heterotopic ossification (HO). definitive diagnosis of HO has been made after the patient's bilateral knee MRI and comparative knee radiography. (Figure 1 and 2) Around the medially-positioned knee joints on both sides, HO was seen. Knee MRI revealed large regions of osteonecrosis in addition to heterotrophic ossification in the bilateral distal femur and proximal tibia.

The patient received indomethacin 100mg/day and alendronate 75 mg/week as initial therapy for HO. The bilateral knee joints, gentle range-of-motion exercises were initiated. One month after beginning the indomethacin treatment, the patient's swelling in both knees lessened, the limitation was shown to retreat by 20 degrees, and walking practice on a parallel bar with a long walking aid and waist belt was initiated.

In the third month of rehabilitation, swelling in the right ankle was observed, and bilateral ankle MRI was performed for the differential diagnosis of osteomyelitis due to decubitus ulcer in the heel area and an increase in acute phase reactants) and HO. MRI of the ankle revealed areas of necrosis in the bilateral distal tibia, bilateral talus, talar dome and 2nd and 3rd metatarsal heads, and diffuse edema in the muscles and fascia of the surrounding soft tissues.(Figure 3) Although ON is most commonly seen in the femoral head and hip joint, ON was not found in the hip MRI of our patient.

During the follow-up of our patient, chest pain and shortness of breath developed, and the patient was diagnosed with pulmonary embolism with the tests. Acute deep vein thrombosis in the popliteal vein was detected in the lower extremity venous Doppler ultrasound performed for the etiology of pulmonary embolism. We wanted to see a thrombophilia panel from our patient because of pulmonary embolism that developed at an early age in the panel was found heterozygous mutations in the MTHFR-C677T, MTHFR-A1298C, PA1-1/4G, Factor XIII-V34L, and GPIIIa-L33P (HPA-1) genes. As a result, the prophylactic dose of enoxaparin was increased.

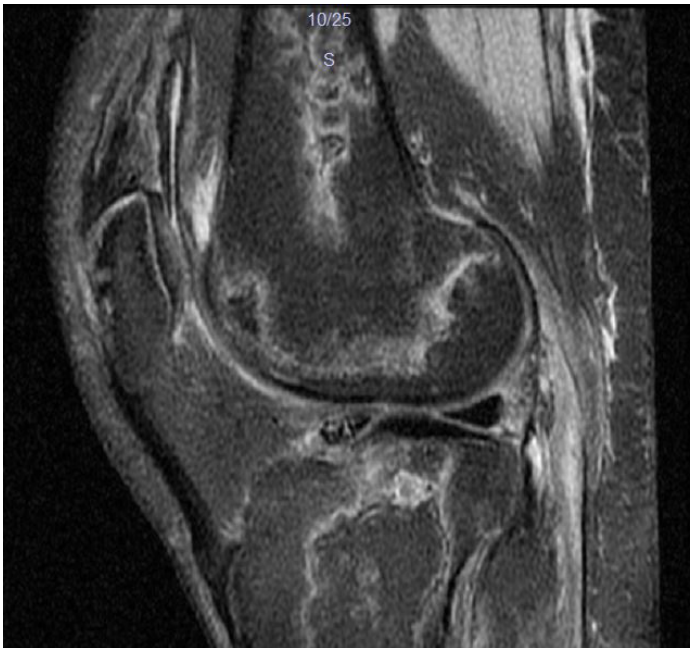

Figure 1. T2 STIR sequences for magnetic resonance imaging diffuse osteonecrosis areas in the proximal tibia and distal femur

Figure 2. Heterotropic ossification on knee radiography, more prominent medially around the bilateral knee joint

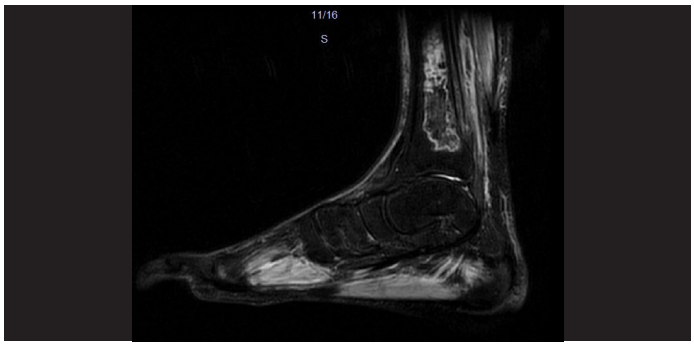

Figure 3. T2 STIR sequences for magnetic resonance imaging areas of osteonecrosis in the distal tibia, talus, talar dome, and metatarsal head

DISCUSSION

Studies have shown that ON can develop locally or multifocally in response to high-dose steroid therapy [5]. Osebold et al. [5] investigation, the effects of spinal cord damage on bilateral humeral head ON were assessed. The importance of various prothrombotic variables that raise the risk of steroid-induced ON was highlighted in this investigation. In this study, the threshold for corticosteroid dose was defined as 2000 mg prednisolone. Our case received 2880 mg of methylprednisolone. Except for steroid usage, which was present in the case study but lowered the threshold for ON in our case, there was no history of spinal canal surgery or alcohol use.

Another study reported that thromboplastic substances produced by injured neural tissue, increased tissue thromboplastin release, and fat embolism that may occur after spinal cord injury may all raise the incidence of ON [6]. In our case, it was discovered that the pre- and postoperative serum lipid levels, platelet count, APTT, PTZ, and fibrin degradation products were all within normal ranges. Our patient did not exhibit any of the risk factors for ON, such as alcoholism, hemoglobinopathies, pancreatitis, radiation, chemotherapy, or storage disorders.

Contrarily, heterozygous mutations in the genes for MTHFR-C677T, MTHFR-A1298C, PA1-1/4G, Factor XIII-V34L, and GPIIIa-L33P (HPA-1) were found in the thrombophilia panel run on our patient. These mutations could raise a patient's relative risk of thrombosis, cardiovascular disease, and cerebrovascular disorders.

It is believed that the use of corticosteroids in individuals with hypercoagulation abnormalities, such as thrombophilia, accelerates the development of ON because these patients are highly sensitive to thrombosis [7]. This study by Shah et al. [7] is supported by mutations found in the thrombophilia panel of our case and MFON that appeared following corticosteroid therapy. MFON developing in patients with spinal cord injury has not been adequately studied in the literature Kuijk et al. [8] gave radiotherapy to patients in order to treat HO that develops after a cord injury, these patients developed ON at the treatment site. At the same time, Kuijk et al. [8] except for the case series that developed ON as a complication after HO treatment, no case was reported on the coexistence of HO and MFON. Our case is the first in this respect.

ON, especially in patients with spinal cord injury in our case as well as shortly after the end of corticosteroid treatment. However, it may also develop in the long term after treatment. On the other hand, especially spinal cord patients may have loss of pain sensation and sensory loss in patients with injuries. They may not report any complaints in tissues that develop ON. Due to the potential of MFON to cause additional disability, especially in young patients, it is of great importance to properly organize weight-bearing exercises in the rehabilitation programme of SCI patients.

Patients' histories of steroid usage should be investigated, hospital records should be reviewed, and in cases of uncertainty, patients should undergo clinical and radiological evaluations.

Yours sincerely.

Keywords: Multifocal osteonecrosis, Spinal cord injury

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How to Cite;

Tikiz C, Özbek İC, Onağ E (2024) Multifocal Osteonecrosis in Spinal Cord Injury. Eur J Ther. 30(3):382-385. https://doi.org/10.58600/eurjther2116

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):386-387.
https://doi.org/10.58600/eurjther2157

Letter to Editor

The Concept of "The Extended Mind" Can Provide A Sound Philosophical Justification for the Academic Use of AI, but with Ethical Precautions!

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Received: 2024-04-24 **Accepted**: 2024-05-14 **Published Online**: 2024-05-17

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Dear editors,

I think the important discussions on artificial intelligence tools in the last few issues of your journal have made important contributions to the literature. We have seen that many authors, especially in the field of medicine and health sciences, have followed and contributed to the topic with interest. In an article that I had previously tried to contribute to, I had argued that we should ask ethical and philosophical questions about the issue depending on the sensitivity of the issue [1]. At this point, it is possible to say that various applications of AI have a significant impact on our lives. In this article, I would like to briefly mention the concept of "the extended mind", which has had a significant impact on fields such as the philosophy of technology and the philosophy of mind with the articles published in 1998 by the important philosophers of technology Andy Clark and David Chalmers, and then I would like to mention that this concept can form a strong basis for academic (and other) uses of artificial intelligence. However, I argue that the uses we can justify with this concept should also be balanced with ethical sensitivity, awareness, and constant questioning.

Andy Clark and David Chalmers argue that we can extend our cognitive functions to the environment, and that we do not need to confine them to the inside of our brains or skulls. In this regard, they state that we can attribute some of our cognitive functions to the tools and devices we use in our relationship with the environment. Thus, the support we receive from outside our brain or from the environment can have an effect on cognitive processes just as it does inside our brain [2]. In this respect, tools such as calculators, reminder applications, notebook and mobile phones perform cognitive functions on our behalf, extending our cognitive capabilities beyond our biological limits, even though they are actually external to us. These tools (not necessarily only physical tools, abstract concepts such as language can also be seen as such) can also become part of our cognitive being. The cognitive contributions of these tools and our given cognitive processes have the possibility of continuous interaction and extension [2].

If we look at the issue of AI and its academic use in terms of the concept of the "extended mind", it can be said that especially the instrumental use of AI applications can be considered as a contribution to our cognitive process. In other words, it may be the case that the cognitive

tasks we impose on artificial intelligence are homologous to the cognitive tasks we can perform. This can basically be seen as a contribution to our mind and its expansion and even development. It is therefore plausible to see applications of artificial intelligence as cognitive tools that can only be used instrumentally in their relation to us, without being subjects in themselves. What I mean here by instrumentality is not necessarily a lower quality in terms of value. It is just used to indicate an ontological difference. In time, AI may also become a fundamental element of our cognitive process in relation to our mind.

Although it seems unlikely today, the most fundamental problem that can be considered in this regard in the future may be related to drawing the boundary between the body and mind that we ascribe to ourselves as subjects and the boundary of the cognitive effect of artificial intelligence as a tool. Although this is an extremely important question, it is beyond the scope of this article for now. In this article, I particularly wanted to emphasize the instrumental use of AI. However, the fact that the use of AI as a cognitive tool can be justified in terms of the "extended mind" concept does not mean that ethical problems will not arise. In particular, the fact that AI is not simply a tool that can be used equidistantly and openly in the real world makes it necessary to have ethical discussions on this issue. In addition, the problem of the transparency of the cognitive processes that we attribute to AI and the cognitive problems that seem to be attributable to AI (bias, etc.) are among the issues that need to be carefully considered. Some of the most fundamental questions that face us academically may be related to the ethical dimension of the production and circulation of knowledge related to AI, the meaning of AI as a means of cognitive enhancement, justice and inequalities. The content of the cognitive contributions of AI in its academic use should be analyzed in detail. Given the speed of AI, the cognitive contributions that humans cannot make can also be seen as a kind of cognitive enhancement tool. In this case, who has or will have this opportunity should be considered, especially in terms of justice and equality. In this respect, the possibility that control over AI applications is predominantly in the hands of private for-profit companies may be a notable area of concern. All these categories of problems require prudence, which is one of the most important concepts of technological ethics [3]. This means that the scientific world should reflect on its actions from the individual to the institutional level and be willing to be responsible researchers.

Yours sincerely,

Conflict of Interest: No conflict of interest.

Funding: No financial support was received..

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How to Cite;

Yıldız A (2024) The Concept of "The Extended Mind" Can Provide A Sound Philosophical Justification for the Academic Use of AI, but with Ethical Precautions! Eur J Ther. 30(3):386-387. https://doi.org/10.58600/eurjther2157

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):388-391.
https://doi.org/10.58600/eurjther2172

Letter to Editor

Sertraline-Induced Stuttering in an Adolescent with Autism Spectrum Disorder

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Received: 2024-05-02 **Accepted**: 2024-05-24 **Published Online**: 2024-05-29

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This case was presented as an oral presentation at the 11th International Medicine and Health Sciences Researches Congress (UTSAK, 24-25 December 2022, Online / ANKARA, only the abstract is published).

ABSTRACT

There is also evidence that stuttering is caused by an adverse reaction to various medications. Antiepileptic drugs, antidepressants, antipsychotics, and methylphenidate have all been linked to drug-induced stuttering. The patient was 13 years old (male) and was diagnosed with autism spectrum disorder, attention deficit hyperactivity disorder, and mild mental retardation. The patient had language development and was able to form sentences of 4-5 words. Atomoxetine 50 mg/day and aripiprazole 15 mg/day treatment was used. Sertraline 50 mg/day treatment was initiated because of repeated questioning, order-symmetry compulsions and repetitive behaviors. Approximately one month after the initiation of sertraline treatment, the patient came for a follow-up visit and it was found that the compulsions of the patient had decreased, but one week after sertraline treatment, it was learned that the patient started to have word blocks, prolongation of words and repetitions during speech. No pathology was found in the examination, hemogram and biochemistry tests, brain MRI and EEG tests. After sertraline treatment was discontinued, the stuttering of the patient gradually decreased and improved within 2 weeks. Both serotonergic and dopaminergic effects of sertraline as well as autism spectrum disorder (white matter anomalies) are thought to contribute to sertraline-induced stuttering.

Keywords: stuttering, sertraline, autism, adolescent, antidepressant

Dear Editor,

Stuttering is defined as a disruption of the normal flow and timing of speech characterized by the repetition of sounds, syllables, or words, the prolongation of sounds, and interruptions in speech known as blocks [1]. Stuttering is usually classified into developmental and acquired stuttering [1]. Acquired stuttering can occur later in life, often as a side effect of certain neurological conditions, medications, or psychological trauma in some cases where stuttering first occurs [2]. There is also evidence that stuttering is caused by an adverse reaction to various medications [1]. Antiepileptic drugs, antidepressants, antipsychotics, and methylphenidate have all been linked to drug-induced stuttering [1, 3]. As a result of drug-induced stuttering, the time between initiation of the causative drug and the onset of stuttering, or between reducing the dosage of the drug and the relief of stuttering, is short. This suggests that drug-induced stuttering may be caused by neurochemical changes in the brain [4]. In

this case report, a 13-year-old patient with autism who started stuttering after sertraline treatment was presented. There are few cases in the relevant literature. To the author's knowledge, this is the first patient who developed sertraline-induced stuttering during adolescence and was diagnosed with autism.

Patient Information

The patient was 13 years old (male) and diagnosed with autism spectrum disorder, attention deficit hyperactivity disorder, and mild mental retardation. The patient also had complained irritability, behavioral problems, and harm to others and objects. The patient was attending individual special education, and no chronic medical disease or speech problems such as stuttering-articulation disorder, were found in the patient's medical history. The patient had language development and could form sentences of 4-5 words. The patient's father had a diagnosis of obsessive-compulsive disorder and there was no family history of stuttering. Atomoxetine and aripiprazole were started as drug treatment and gradually increased to 50 mg/day and 15 mg/day, respectively. The patient was followed up regularly in our outpatient clinic for about 5 months. Sertraline 50 mg/day treatment was initiated because of repeated questioning, order-symmetry compulsions, and repetitive behaviors. Approximately one month after sertraline treatment, the patient came for a follow-up visit and it was found that the patient's compulsions had decreased. However, one week after sertraline treatment, it was learned that the patient started having word blocks, word prolongation and repetitions during speech. It was learned that these complaints occurred almost every day, often during speech. Stuttering was considered in the patient who was also observed with these complaints during the interview. Clonic stuttering was considered in the case and no movement disorder accompanying stuttering was observed or detected. In the evaluation, it was not found that there was no sibling birth, moving, loss, or any stressful situation or change at school or home before stuttering**.** He was referred to Ear-Nose-Throat and Pediatric Neurology physicians for organic etiology. No pathology was found in the examination, hemogram and biochemistry tests, brain MRI and EEG tests. Stuttering was thought to be due to sertraline and sertraline treatment was discontinued. After sertraline treatment was discontinued, the patient's stuttering gradually decreased and improved within 2 weeks. The patient was then started on fluoxetine treatment and no stuttering-like side effects were observed in follow-up. The patient received fluoxetine treatment for about 6 weeks, but his symptoms persisted, and fluoxetine treatment was discontinued and escitalopram treatment was started. With escitalopram 20 mg/day treatment, obsessive-compulsive symptoms decreased, and no stuttering-like side effect was observed in follow-up. Written and informed consent was obtained from the patient's parents.

DISCUSSION

Stuttering has not been sufficiently characterized in terms of its etiology and pathogenesis. A number of factors contribute to stuttering, including differences in brain anatomy, particularly in the auditory and motor cortex and the substantia nigra. In addition, there are differences in dopaminergic function and regulation [5]. Medications can treat stuttering, but they can also cause stuttering as a side effect. For example, although there are promising results with atypical antipsychotic drugs such as risperidone and olanzapine in the treatment of stuttering [6], there are also case reports of induced (antipsychotic drugs) by drugs used in the treatment of stuttering [7].

Signals are sent from the basal ganglia to the thalamus to stimulate the cerebral cortex to initiate desired movements. This is based on motor, sensory, and cognitive input. Signals received by the input nuclei of the basal ganglia are transmitted through two pathways: a) directly and b) indirect. The direct pathway stimulates the cerebral cortex and activates the correct motor program, while the indirect pathway inhibits the cerebral cortex and all competing motor programs. Dystonia, dyskinesia, and stuttering can all be caused by disruption of these two pathways' coordination and cross-talk. Therefore, both increased and decreased dopamine neurotransmission in the striatum can disrupt the balance between direct and indirect pathways, leading to stuttering [4]. This suggests that an imbalance in dopamine levels involved in speech coordination may trigger various speech disorders such as stuttering [4]. Currently, in the etiology of drug-induced stuttering, drugs that potentiate the dopaminergic system or affect neurotransmission in the central nervous system are particularly emphasized [3]. However, it has been stated that in addition to increased dopamine levels, decreased GABA, the anticholinergic properties of drugs and changes in serotonin levels may also contribute to the development of drug-induced stuttering [1]. In many reports, selective serotonin reuptake inhibitors (SSRIs) have also been implicated, suggesting serotonergic mechanisms may be involved [8]. In a review of the literature, the drugs most associated with drug-induced stuttering were methylphenidate, topiramate and olanzapine, respectively [3]. However, there are some reported cases of stuttering associated with antidepressant drugs and the drugs with the highest relative risk ratio among

antidepressants are venlafaxine, citalopram and mirtazapine [3]. Sertraline is an antidepressant in the class of SSRIs with inhibitory effects primarily on presynaptic serotonin reuptake [9]. Several different mechanisms associated with sertraline-induced stuttering may be involved in this effect. Firstly, sertraline-induced stuttering may also be triggered by serotonergic inhibition of dopaminergic neurons. The ventral tegmental area contains these neurons' cell bodies. As a result, sertraline and other selective serotonin reuptake inhibitors cause stuttering by inhibiting dopamine pathways in the nigrostriatum [4]. SSRIs also cause more akathisia than other antidepressants, and akathisia is common in drug-related stuttering [8]. This supports that a similar mechanism may contribute to sertraline-induced stuttering [8]. It is thought that this mechanism may be related to stuttering by disrupting the dopamine balance involved in speech coordination. Second, sertraline also has minimal effects on dopamine levels and research has shown that it has greater dopaminergic activity than other drugs in the same SSRI category [10]. Sertraline increases dopamine levels in the striatum and nucleus accumbens by inhibiting dopamine transporters and this effect is higher than other antidepressants [10]. Considering that stuttering symptoms worsen with dopamine agonists and improve with dopamine antagonists [6], this effect of sertraline causing dopamine elevation may be related to stuttering and may be thought to cause stuttering by contributing to dopamine elevation, which is the most emphasized in the etiology of stuttering.

However, an alternative mechanism may also be involved in sertraline-induced stuttering in children with ASD. White matter (WM) abnormalities may also affect the connectivity between different areas of the brain involved in speech's motor control. Myelinated axons, which make up WM tracts, transmit signals between different brain regions, so they can coordinate their communication and functions [11]. Stuttering may result from the disruption of signal transmission between different areas of the brain that control speech and motor control by an agent that disrupts the normal activity of one or more neurotransmitters in the white matter [4]. Furthermore, abnormal functional connections in autism spectrum disorder have been shown to be defects in the integrity of white matter tracts, which include a collection of myelinated axon bundles that allow fast and efficient neuronal communication between different brain areas [12]. In patients with an underlying disorder, drugs that disrupt the normal balance of neurotransmitters in white matter may exacerbate white matter dysfunction.

In addition to sertraline, our patient was also receiving atomoxetine and aripiprazole treatment. Aripiprazole is a partial agonist of 5HT-1A and dopamine D2 receptors and antagonist of 5HT-2A receptors in the central nervous system. Aripiprazole and other antipsychotic drugs may cause extrapyramidal side effects and stuttering by disrupting the balanced and coordinated activity of dopamine pathways. In addition, increased dopamine neurotransmission in the prefrontal cortex as a result of serotonergic effects of aripiprazole may also lead to stuttering. Atomoxetine acts by increasing noradrenaline and dopamine concentrations in the prefrontal cortex. Rather than dopaminergic effects of atomoxetine, it increases activity in the subthalamic nucleus and consequently decreases the excitatory activity of the thalamocortical pathway [4]. This may cause stuttering as a result of inappropriate activation of orofacial muscles. In our case, the use of multiple drugs with activity on the dopaminergic pathway may have caused stuttering by affecting the dopamine balance.

In the present case, stuttering developed after initiation of sertraline treatment and gradually decreased after discontinuation of the drug. In 55.8% of cases with drug-induced stuttering attacks, the drug thought to cause stuttering was discontinued and stuttering was significantly reduced or completely recovered in all cases after discontinuation of the drug [4]. This finding is consistent with the improvement in stuttering after discontinuation of sertraline in the present case. This case report presents possible evidence for sertraline-induced stuttering and its etiology. Both the serotonergic and dopaminergic effects of sertraline as well as autism spectrum disorder (white matter anomalies) are thought to contribute to sertraline-induced stuttering. There are a limited number of studies on sertraline-induced stuttering in children and adolescents. Children in this age group with underlying disorders such as autism spectrum disorder are more susceptible to side effects, and should be monitored more closely for side effects such as stuttering.

Yours Sincerely,

Acknowledgements: None.

Conflicts of interest: The author declare not to have any conflict of interest.

Funding sources: No funding source was utilized for the present study.

Ethics Approval: Ethics committee approval was not obtained because it was a case report. Written and verbal consent was obtained from the parents of the patient.

Author Contributions

Conceptualization: M.Ö.; Data acquisition: M.Ö.; Supervision: M. Ö.; Writing—original draft: M.Ö.; Writing—review & editing: M.Ö.

* This case was presented as an oral presentation at the 11th International Medicine and Health Sciences Researches Congress (UTSAK, 24-25 December 2022, Online / ANKARA, only the abstract is published).

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How to Cite;

Öztürk M (2024) Sertraline-Induced Stuttering in an Adolescent with Autism Spectrum Disorder. Eur J Ther. 30(3):388-391. https://doi.org/10.58600/eurjther2172

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):392-394.
https://doi.org/10.58600/eurjther2229

Letter to Editor

Comments on "Clinicopathological Features of Elderly Patients with Colonic Volvulus"

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Received: 2024-06-09 **Accepted**: 2024-06-13 **Published Online**: 2024-06-26

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Dear Editor,

A recent article *"Clinicopathological features of elderly patients with colonic volvulus"* by Gül et al. [1] evaluated some epidemiologic, diagnostic, therapeutic, and prognostic characteristics of 44 patients with colonic volvulus including sigmoid volvulus (SV). I thank the authors for their interesting research [1]. I would like to make some additional contributions on this clinically valuable topic.

Eastern Anatolia, where I practice, is an endemic area of SV, which is the most common type of colonic volvulus [2]. My colleagues and I have 57.5-year (between June 1966 and January 2024) and 1,076-case experience with SV, which comprises the largest single-centre SV data over the world [3]. Based on this comprehensive experience, my comments relate to some characteristics of SV.

First, the authors presented no demonstrative blood test in patients with SV [1]. Although high white blood cell count and neutrophil ratio may suspect bowel ischemia, and electrolyte imbalance may reflect an obstruction, there is no routine blood test to diagnose SV [4, 5]. Abdominal X-ray radiographs suggest SV by demonstrating omega-like dilated sigmoid segments (Fig. 1.a) with 57%-90% of diagnostic success rate and computed tomography (CT) helps to diagnosis by presenting mesenteric whirl sign in addition to X-ray findings (Fig. 1.b) with 85%-98% of diagnostic accuracy rate, both of which used by the authors [2, 5]. However, magnetic resonance imaging (MRI) is a critical alternative to CT in pregnant women by presenting similar findings (Fig. 1.c) and correct diagnosis rates [2, 6]. Similarly, endoscopy, preferably flexible procedure, is not only a therapeutic but also a diagnostic procedure by demonstrating a spiral-like obstructive sigmoid lumen (Fig. 1.d) in 75%-98% of SV cases [2, 7]. In our series, X-ray radiographs were diagnostic in 68.8% (636/925) of the patients, while the diagnostic accuracy rates of CT, MRI, and endoscopy were 98.0% (147/150), 95.7% (43/46), and 98.7% (150/152), respectively.

Second, although the authors demonstrated statistically higher mortality rates in patients with American Society of Anesthesiologists (ASA) score 4 when compared with that of cases

with ASA scores 2 and 3 (57.9% vs. 0% and 9.5%, p<0.05), they presented no statistically significant relations between mortality and age, comorbidity, and bowel perforation [1]. However, advanced age, comorbid diseases, and peritonitis arising from bowel perforation are well-known bad prognostic factors in SV [8-10]. Hence, in our series, among decedent 85 (17.4%) of surgically treated 488 patients, 66 patients (77.6%) were over 60 years old, and 39 cases (45.9%) were older than 70 years. Similarly, serious comorbidity and bowel perforation were determined in 58 (68.2%) and 8 (9.4%) of our deceased cases, respectively.

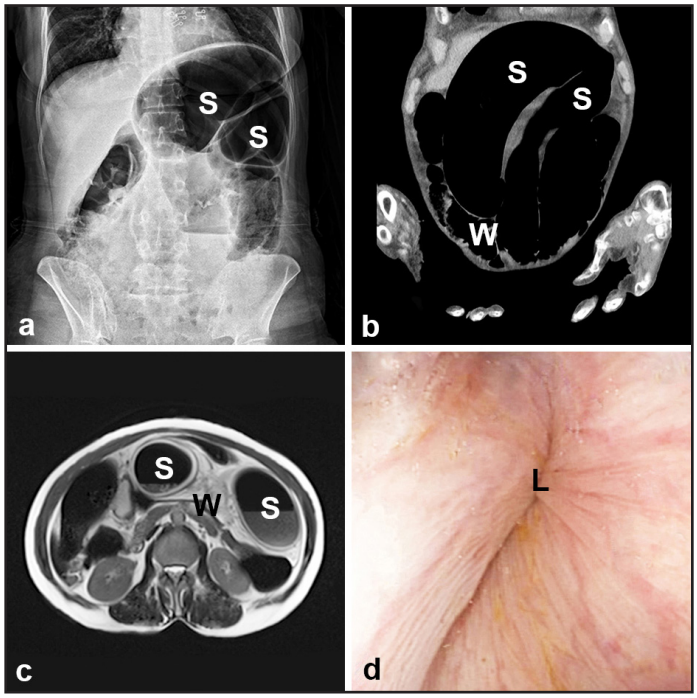

Figure 1. a. Abdominal X-ray radiograph of sigmoid volvulus **b.** Abdominal coronal computerized tomography image of sigmoid volvulus. **c.** Abdominal axial magnetic resonance image of sigmoid volvulus. **d.** Endoscopic appearance of sigmoid volvulus (S: dilated sigmoid colon segments, W: mesenteric whirl sign, L: Spiral-like obstructive sigmoid lumen).

As a result, I suggest diagnostic endoscopy in colonic obstruction-suspected cases as the primary diagnostic procedure, while I offer MRI in the diagnosis of pregnant women with clinical features of colonic obstruction. Additionally, I think that serious comorbidity and related high ASA scores as well as advanced age and bowel perforation are non-ignorable parameters affecting poor diagnosis.

Best Regards,

Conflict of interest: The author declares that he has no conflict of interest.

Funding: None.

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Atamanalp C (2024) Management of Sigmoid Volvulus: A Literature Review. Ibnosina J Med Biomed Sci 16:5-9. https://doi.org/10.1055/s-0043-1776142

How to Cite;

Atamanalp SS (2024) Comments on "Clinicopathological Features of Elderly Patients with Colonic Volvulus". Eur J Ther. 30(3):392-394. https://doi.org/10.58600/eurjther2229

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):395-399.
https://doi.org/10.58600/eurjther2138

Letter to Editor

Young Minds, Rare Finds, and the Path to Publish Case Reports

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Received: 2024-04-12 **Accepted**: 2024-04-26 **Published Online**: 2024-04-27

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Abstract

A case report (CR) is a type of medical literature that demonstrates the scientific documentation of a rare disease/phenomenon, an unusual presentation of common diseases, or an innovative treatment for the disease. CRs can serve as an impetus for further research, prompting investigators to explore the potential associations, mechanisms, or therapeutic interventions suggested by individual case observations. However, emerging researchers often encounter various challenges while documenting CRs for publication, including limited experience, difficulty navigating relevant literature, ethical considerations, and publication barriers. This article focuses on empowering emerging researchers for the medical writing of CRs by providing a roadmap from observation to publication in a minimum duration, along with the implication of artificial intelligence (AI) in CR writing, highlighting AI's potential to streamline drafting processes while addressing technical limitations, biases, and ethical concerns associated with its use. Thus, equipping emerging researchers with the necessary tools and resources, fostering confidence and competence by demystifying the CR writing process, and empowering aspiring authors to contribute meaningfully to the scientific literature.

Keywords: Case report, CARE Guidelines, Medical Writing, CARE Extension, Research Publication, Single-subject research, health sciences

Dear Editor,

Medical writing of case reports (CRs) represents the foundation of the hierarchy of the evidence and serves as a beneficial exercise in learning how to write scientifically due to the similarity of the basic methodology. Congruently CRs reflect the pioneering effort for healthcare professionals to get articles published in medical journals [1]. A CR provides an elaborative description of a patient's unique clinical presentation, diagnosis, treatment, and follow-up care. The history of CRs can be traced back to Hippocrates providing description of scientific information regarding disease which can be overlooked in various types of clinical trials [2].

CRs play a crucial role in the generation and testing of hypotheses. They can serve as the impetus for further research, prompting investigators to explore potential associations, mechanisms, or therapeutic interventions suggested by individual case observations. They serve as educational tools for students, residents, and practicing clinicians, facilitating

the dissemination of knowledge and the development of clinical acumen [3]. CRs are outcome-oriented exercises, as emerging researchers evaluate patients, document positive findings, and are encouraged to disseminate these findings through publication. This method not only improves comprehension of practical scenarios but also highlights the development of innovative strategies and the broadening of knowledge within the field through published case studies [4].

Medical writing of CRs requires presentation of the clinical findings in a clear, concise, and scientific manner. This synergy of artistic and research skills are essential for career advancement which can only be achieved through consistent publication of CRs, as it provides practical experience in conducting literature reviews, data analysis, and manuscript writing. In addition, the publication of CRs early in the career can enhance popularity and recognition in the scientific community as a researcher, expert, or a clinician related to a specific field. It motivates individuals to highlight their research skills, clinical expertise, and accomplishments offered towards the medical education. Additionally, it facilitates access for participation in conferences, associated projects, and interdisciplinary research collaborations, all of which are crucial for career advancement and professional growth fostering collaborations with peers, experts, and mentors leading to networking opportunities [5,6]. However, emerging researchers may encounter various challenges during the implementation of CR writing which commonly include accessing of appropriate literature, issues related to ethical considerations, inadequate experience, and publication barriers. These challenges can be addressed by providing the techniques for literature review, including ethical principles, emphasizing key considerations, and guidelines for manuscript formatting to ensure the quality and integrity of CRs. Moreover, practical tips and strategies from formulating a research question to navigating the publication process is essential for boosting competence and confidence by organizing and simplifying the process of CR writing and influencing researchers to offer significant contributions to the scientific literature [3,7]. The subsequent sections provide comprehensive guidance and practical advice along with the recommendations to assist emerging researchers at each stage of the CR writing process.

Emphasizing the Purpose

While writing a medical CR, it is important to determine whether the case aims to highlight a rare or uncommon condition or to describe a novel treatment approach. Additional common reasons for publishing CRs involve the description of an unexpected correlation between symptoms or diseases, unusual or uncommon features of a disease, variations in anatomical structures, novel insights into the pathophysiology or side effects of a disease, an unexpected event during patient observation or treatment, and innovative therapeutic approaches. Many journals publish CRs that describe uncommon observations, adverse reactions to therapies, queries regarding established theories, demonstration of new theories, unique combinations of conditions causing confusion, and personal impacts [8]. Therefore, a clear purpose guides the content and structure of the CR.

Framework for Composition

Enhancing the Quality and Transparency Of Health Research (EQUATOR) network provides guidelines for CR documentation for various healthcare professions consisting of CAse REport (CARE) guidelines, Surgical CAse REport (SCARE), HOMeopathic clinical CASE reports (HOM-CASE), and CARE guidelines adapted for Therapeutic Massage and Bodywork (TMB) case reports. Similarly, CARE-radiology has been developed for reporting radiology-related CRs [9] and an extension of CARE guidelines for PHYsiotherapy CAse REports (PhyCaRe) is currently under development [10]. Most of the CRs follow a standard structure, including a title, an abstract, an introduction, a case presentation, a discussion, and a conclusion section while according to the journal guidelines, some may demonstrate a literature review [8]. Whereas, a universally accepted recommended strategy to write a manuscript begins with methodology, followed by results, introduction, discussion, conclusion, title, and abstract sections which can be inculcated for drafting of the CRs [11]. Therefore, for writing the CRs the sequence should be the case presentation section, followed by the introduction, discussion, conclusion, title, and abstract sections. However, while publishing, the CR can be arranged into the standard structure as most of the journals adhere to these guidelines for quality and presentation and follow CARE guidelines [8,12].

Before initiating the writing of the CR, it is essential to obtain informed consent from the patient or the patient's legal guardian as it is required by all the journals during the CR submission. This ensures that the patient is informed of how their personal information including images will be used and allows the patient to opt out of the publication process. The patient must be

competent and should not be forced into giving their informed consent [8].

Following this, gathering of all the relevant information and drafting of the CR should be commenced which includes detailed medical history of the patient, physical examination findings, diagnostic assessment, treatment plan, and records related to follow-up visits along with the images associated with the case for adequate and accurate documentation of the patient's care. However, it should be taken into consideration that the medical notes disappear after the patient is discharged and are generally difficult to retrieve [13].

The title should be a clear and short description of the case focusing primarily on the diagnosis or the novel intervention and should mention the word "case report" [2,14]. The abstract part should be a concise and condensed summary of the CR that incorporates the key components of the main text [2,13] and correspondingly, keywords should be included since these terms are essential for easy online retrieval and indexing. Emphasis on the abstract and the title should be made as these sections primarily depend on the other elements of the CR. The introduction section should describe background information on the condition being described and the purpose of the CR, followed by the case presentation section which can be further segregated into various subheadings that encompass patient information, physical or clinical examination, timeline, diagnostic investigations, differential diagnosis, therapeutic intervention, follow-up, and outcomes. This should be supported with appropriate images consisting of patient photographs, radiographic images, or diagrams of diagnostic and therapeutic interventions as it can help to illustrate the key findings. To prevent errors during submission and publication, the photographs should be of excellent quality and resolution. The discussion section should compare and contrast the CR with the published literature and briefly summarize with contemporary references. Additionally, to ensure validity, uniqueness, and accuracy it should inculcate insights into the diagnosis, treatment, and outcome. Moreover, it should signify why this CR is important for the medical community and its implication on current clinical practice along with the limitations and future applications. Lastly, the conclusion section should summarize how the CR contributes to the medical literature highlighting the learning points or take away lessons [2].

The patient perspective section is optional and varies from journal to journal. However, it should be included, as this section provides an opportunity for patients to describe the case from their perspective. The patient is encouraged to elaborate on their symptoms, explain what initiated seeking medical advice, how effective the therapeutic intervention is, and how the issue reflects in the current situation. However, the section should not include identifying information. The patient perspective is important as it contributes to medical education and clinical decision-making [2].

The reference section should cite relevant literature adhering to the journal's referencing style guidelines. Ensure accuracy and currency of references (referring to last five years), prioritizing primary sources and influential works where applicable. Generally, the standard recommendation is of 15 references for CRs; however, journals may accept submissions with more references, specifically, if there is an extended literature review [2].

After writing and structuring the initial draft, seek peer feedback from colleagues, mentors, or an experienced editor to ensure scientific integrity, accuracy, and clarity. Following this, before proceeding for submission all the remarks and recommendations should be addressed for improvisation of the CR [3].

Augmenting Artificial Intelligence

Artificial intelligence (AI) technologies utilize advanced algorithms, natural language processing (NLP), and machine learning techniques to assist researchers and clinicians at different phases of CR writing by offering automated literature searches along with extraction of the data to organised manuscript drafting and real-time feedback. Thus, revolutionizing the field of medical writing by providing innovative methods for optimizing the process of CR drafting more quickly and efficiently.

Additionally, these technologies are scalable and adaptable to different research settings and disciplines, making them useful in various types of clinical specializations and research fields. However, by integrating patient-specific data, AI technologies may further assist clinicians in modifying interventions according to the unique characteristics and needs of each patient, thereby improving outcomes and patient satisfaction. Moreover, these tools may provide paraphrasing suggestions, grammar corrections, and automated templates to improve coherence and clarity. As a result, in accordance with the publication

requirements of the peer-reviewed journals, AI technologies empower emerging researchers to produce high-quality CRs [15–17].

However, AI tools exhibit certain technical challenges. These include biased data quality, specific knowledge gaps related to the context of the CR, and clinical reasoning issues, leading to misinterpreted or inaccurate conclusions. Similarly, it could result in a decrease in analytical or critical thinking of the researchers due to over-dependency on AI tools as there is a risk that the researchers may get acquainted and accept the results which are AI-generated without verifying their accuracy. Moreover, the researchers must ensure that the application of AI in CR writing aligns with ethical guidelines and regulations governing protected health information and the use of patient data which involve informed consent, patient confidentiality, and data privacy. Additionally, the researchers must carefully examine the universality and applicability of AI-generated outcomes to different populations and contexts as AI algorithms trained on specific datasets or populations may lack generalizability to other settings or patient populations. Furthermore, AI tools should be retrained routinely as most of them are not updated frequently with the most recent information [16,18].

To summarize, it is crucial to strike a balance between the integration of AI's potential and appreciating the significance of critical thinking, ethical issues, and human creativity. However, patient well-being, integrity of medical information, and the overall enhancement of healthcare practices must be carefully considered and prioritized. By implementing this, emerging researchers can benefit from AI while maintaining the highest quality of medical writing and patient care.

Navigating for Publication

Once the CR has been edited and amended, it is ready to be submitted to a medical journal for publication. Prior to submission, the CR should be formatted according to the author's guidelines which should be thoroughly checked for the respective journal. In recent times, many journals dedicated only to publishing CRs have been launched. However, for publication of the CRs, it is important to focus on journals involving universally accepted databases.

Before submitting, ensure that the journal has clear peer review guidelines, the publisher is easily identified and can be contacted, the journal's website is updated and the latest articles are easily accessible as these elements are important to avoid predatory journals. Additionally, to inspect the current indexing of the journal the researchers should verify both the journal and the database. Furthermore, open-access journals are recommended for publication since readers can easily access the CR. However, high publication cost presents a challenge for researchers from low-income countries, although depending on the country, majority of the journals offer waivers and discounts [19–21].

Regards,

Disclosure: No financial support was provided to conduct this study

Conflict of Interest: The authors do not have any competing interests.

Author's Contribution: The final manuscript was reviewed and approved by all the authors.

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How to Cite;

Pashine AA, Naqvi W.M, Arora S.P. (2024) Young Minds, Rare Finds, and the Path to Publish Case Reports. Eur J Ther. 30(3):395-399. https://doi.org/10.58600/eurjther2138

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):400-408.
https://doi.org/10.58600/eurjther2034

Review Article

Optimizing Patient Outcomes in Orthognathic Surgery: A Proposed Nutritional Protocol for Weight Loss Control and Bone Formation

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Received: 2024-01-27 **Accepted**: 2024-03-27 **Published Online**: 2024-03-29

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ABSTRACT

Objective: The primary objective of this research was to conduct a comprehensive literature review, offering an in-depth examination of the nutritional considerations associated with orthognathic surgery and suggest a perioperative nutritional protocol for enhanced recovery.

Methods: To achieve this objective, the authors rigorously examined existing literature while adhering to the guidelines outlined in PRISMA-ScR. The scope of eligible studies encompassed various types, with the exclusion of case reports and reviews. The research applied specific inclusion criteria, concentrating on the nutritional aspects relevant to perioperative and/or postoperative phases of major maxillofacial surgery.

Results: A total of 39 articles were identified that met the screening criteria. These articles were then used to generate a discussion and propose a protocol aimed at reducing body weight loss following major maxillofacial surgery and improving bone formation post-osteotomies.

Conclusions: While the realm of maxillofacial surgery sees significant advancements in other fields, there exists a noticeable gap in addressing the nutritional status of surgical patients. This oversight can potentially lead to suboptimal postoperative outcomes. Recognizing the pivotal role of nutrition in enhancing surgical results, this paper emphasizes the importance of maintaining optimal nutritional status among orthognathic surgery patients.

Keywords: Maxillofacial surgery; maxillofacial surgical procedures; treatment outcome; dietary supplements

INTRODUCTION

A diverse range of maxillofacial surgeries are conducted globally on a daily basis, encompassing procedures ranging from third molar extractions to complex maxillofacial reconstructions and orthognathic surgeries. The existing body of literature is abundant in discussions of virtual planning, [1] emerging technologies, [2] and pharmaceutical advancements [3] that contribute to enhancing the safety of surgical procedures and reducing postoperative discomfort for patients. Regrettably, there is a notable dearth of publications addressing the nutritional status of these surgical patients. This gap in research hinders a comprehensive understanding of how nutritional factors can further optimize the outcomes of maxillofacial surgeries.

Nutritional consultations, pre-operative assessments, and the consideration of mineral and vitamin supplementation often do not receive the requisite emphasis in the research and surgical community. [4] This oversight has the potential to result in suboptimal postoperative results. [5] While numerous studies have contributed valuable insights into the significance of nutrition in various surgical contexts, [6–9] there remains a notable paucity of literature dedicated to this topic in the realm of maxillofacial surgery. [10–13] Recognizing the foundational importance of staying current with developments in this area, the need for constant updates and research on this subject becomes apparent, as it is essential for achieving even more improved surgical outcomes. [14]

Main Points:

- Nutritional consultations, pre-operative assessments, and the consideration of mineral and vitamin supplementation often do not receive the requisite emphasis in the research and surgical community.
- While numerous studies have contributed valuable insights into the significance of nutrition in various surgical contexts, there remains a notable paucity of literature dedicated to this topic in the realm of maxillofacial surgery.
- Proposition of a protocol aiming on reducing body weight loss following major maxillofacial surgery and improving bone formation post-osteotomies.
- Topics such as perioperative nutritional care, weight imbalance due to involuntary loss, physical and functional evaluations, electrolytes, vitamins and bone physiology.

Hence, the primary objective of this paper is to delve into the crucial significance of maintaining an optimal nutritional status among individuals undergoing orthognathic surgery. Furthermore, the secondary aim of this paper is to put forward a comprehensive perioperative nutritional protocol tailored specifically to this patient population, with the ultimate goal of augmenting favorable surgical outcomes.

MATERIALS AND METHODS

The information presented in this article was compiled through a comprehensive examination of existing literature, following the PRISMA-ScR guidelines. [15] A specific search strategy was employed by two independent reviewers (BL and RG), who conducted searches in online databases, including PubMed, Scopus, and Web of Science (WoS). This search strategy incorporated the use of keywords such as “nutrition,” “diet,” “dietetic,” “surgery” and “maxillofacial surgery.” All types of studies related to maxillofacial surgery, except for case reports and reviews, were considered for inclusion. Additionally, a manual search of the databases was conducted to identify articles that might not have been initially captured, by reviewing the references of the included articles. There were no restrictions imposed on language or publication year.

The titles and abstracts of the search results were carefully assessed to determine their relevance to the study. Subsequently, selected articles underwent a full-text screening, during which the authors thoroughly examined and extracted pertinent data.

This study involved a critical review of publicly available electronic sources and did not entail the use of specific patient information. Consequently, it was granted exemption from institutional review board approval.

RESULTS

A total of 39 articles were identified that met the screening criteria. These articles were then used to generate a discussion and propose a protocol aimed at reducing body weight loss following major maxillofacial surgery and improving bone formation post-osteotomies. Topics such as perioperative nutritional care, weight imbalance due to involuntary loss, physical and functional evaluations, electrolytes, vitamins and bone physiology was added. This protocol was organized into a table format and is presented as Table 1.

Table 1. Optimal Nutritional values for weight loss control and bone formation

Body Mass Index (BMI)	18.5 to 24.9 kg/m^2
Calcium (Ca)	1,000 to 1,300 mg/day
Sodium (Na)	200 mg/day
Magnesium (Mg)	310 to 420 mg/day
Phosphorus (P)	700 mg/day
Potassium (K)	4,700 mg/day
Iron (Fe)	Men – 8 mg/day Women – 18mg/day
Vit. A	Men – 900 mcg/day Women – 700 mcg/day
Vit. B_{12}	Men – 2,4 mcg/day Women – 2,4 mcg/day
Vit. D	Men - 600 mcg/day Women – 600 mcg/day
Vit. C	Men - 90 mcg/day Women – 75mcg/day
Vit. K	Men – 120 mcg/day Women – 90 mcg/day
Vit. B_6	Men – 1.3mcg/day Women – 1,3 mcg/day
Vit. E	Men – 15mcg/day Women – 15 mcg/day

DISCUSSION

The correct distribution and safe administration of nutrition and metabolic support are critical matters of life and death in surgical and intensive care units. It's important to note that obese patients face increased surgical risks, as indicated by Blackbur in 2010. [16] While surgical complications often relate to the severity of the underlying disease and the specific surgical procedure, malnutrition can exacerbate various complications. Generally, patients who are well-nourished tend to handle major surgeries more successfully compared to those who are severely malnourished.

Perioperative Nutritional Care

The traditional practice of instructing patients to fast from midnight before surgery, known as "nothing by mouth" (NPO), has been phased out in many medical settings. Historically, the American Society of Anesthesiologists recommended that patients refrain from consuming solid food for 8 hours before surgery and from drinking fluids for 6 hours before anesthesia induction. This approach aimed to reduce the risk of aspiration and regurgitation. However, two Cochrane reviews have suggested that patients can safely consume fluids a few hours before surgery without increasing the risk of complications. [17, 18]

Furthermore, the use of carbohydrate-rich beverages before surgery has been shown to improve glycemic control and reduce nitrogen loss, lean body mass, and muscle strength after abdominal and colorectal surgery. [19] In emergency cases, preoperative fasting is often not possible, and surgery must be scheduled urgently, with patients treated as if their stomachs are full. [20]

For postoperative patients in critical condition admitted to the ICU, early energy intake is recommended unless it is absolutely contraindicated. [21] This practice has been associated with reduced infection rates and shorter hospital stays. [22] Additionally, using nutritionally enhanced formulas has been linked to fewer complications in surgical patients. [23]

In cases where oral feeding is not feasible or prolonged total parenteral nutrition (TPN) is expected, an enteral feeding access device should be placed during surgery. Studies are underway to evaluate the benefits of combining fish oil with nutritional therapy to enhance surgical outcomes in older adults after major surgery, with initial results showing promise in reducing systemic inflammation, lean muscle loss, and weight loss. [24] Traditionally, patients have progressed from simple liquids to blended foods and finally to solid foods over several meals after surgery. However, there is no physiological reason to delay the introduction of solid foods once the gastrointestinal tract is functioning well and the patient is tolerating liquids. [22] Surgical patients can be transitioned to a regular diet of soft solid foods instead of being limited to a liquid-only diet.

Whenever possible, vitamin and mineral levels should be assessed through blood tests, and any deficiencies should be addressed with supplementation before surgery. In addition to maintaining a well-balanced nutritional intake before and after surgery, the potential for oral supplementation should be considered.

Weight Imbalance Due to Involuntary Loss

The term "underweight" is used to describe individuals who are 15% to 20% or more below the established weight standards. Because being underweight often indicates an underlying health

issue, it should be assessed from a clinical perspective. A low BMI (less than 18.5 kg/m2) is linked to a higher risk of mortality, especially in the elderly, compared to those with an ideal BMI (ranging from 18.5 kg/m2 to 24.9 kg/m2). [25]

Malnutrition can lead to reduced functioning of the pituitary, thyroid, gonads, and adrenal glands. Other risk factors include decreased energy levels, susceptibility to injury and infections, as well as distorted body image and other psychological challenges. Underweight or unintentional weight loss can result from various factors: (1) inadequate consumption of oral food and beverages, insufficient to meet daily activities; (2) excessive physical activity, such as compulsive sports training; (3) insufficient capacity for absorbing and metabolizing consumed food; (4) hypercatabolic diseases that raise metabolic rates and energy requirements, like cancer, HIV, or hyperthyroidism; or (5) heightened energy expenditure during psychological or emotional stress. [25]

Addressing the underlying cause of involuntary weight loss or low BMI should be the primary focus of management. Nutritional therapy and dietary adjustments can be effective when combined with treating the underlying condition. If inadequate oral food intake is the cause of underweight, activity modification and psychological counseling, if necessary, should be considered. A thorough history can help identify eating habit deficiencies. Meals should be planned and enjoyed in a relaxed manner rather than rushed. Individuals who are underweight may need encouragement to eat, even when not hungry. The key is to personalize the program with foods the individual enjoys, incorporating regular meals throughout the day. Snacks are often necessary to increase energy intake. [25]

Frequently, liquid supplements taken with or between meals are convenient, nutritious, and easy to prepare and consume. Ideally, the diet should provide approximately 30% of kilocalories from lipids, primarily from mono- or polyunsaturated sources, and at least 12% to 15% of kilocalories from protein. Encouraging the use of common vitamin and mineral supplements can also be beneficial. In addition to meeting estimated energy needs for the current weight, an additional 500 to 1,000 kilocalories per day should be planned for weight gain. This increase in intake should be gradual to prevent gastric discomfort, discouragement, electrolyte imbalances, and cardiac issues. It's advisable to consult with nutritionists to estimate energy requirements and assess a dietary plan. [25]

Physical and Functional Evaluations

Body weight can be assessed and understood through various methods, such as BMI, standard weight, and the actual measured weight. The actual body weight is the weight recorded during the examination and can be influenced by changes in an individual's fluid levels. A reduction in weight may indicate dehydration, but it could also suggest an immediate inability to meet nutritional requirements, which is a sign of potential nutritional risk. The percentage of weight loss is a strong indicator of the severity and extent of an individual's illness. Blackburn's formula from 1977 [26] is a valuable tool for calculating recent weight loss:

- Significant weight loss: A 5% decrease in weight within one month, a 7.5% decrease within three months, or a 10% decrease within six months.
- Severe weight loss: Weight loss exceeding 5% within one month, more than 7.5% within three months, or surpassing 10% within six months.

Body Mass Index

Another approach for assessing whether an adult's weight is appropriate for their height is by using the Body Mass Index (BMI) as described by Kesari and Noel in 2023. [27] BMI is determined by considering weight and height measurements and serves as an indicator of potential overnutrition or malnutrition. What sets BMI apart is its ability to account for differences in body composition by measuring adiposity and relating it to height, thus reducing the reliance on body frame size, as highlighted by Stensland and Margolis. [28] BMI exhibits the weakest correlation with body height but the strongest correlation with independent measures of body fat in adults. [29, 30] The formula for BMI calculation is as follows: BMI = Weight (kg) ÷ Height (m)^2.

According to established standards, an adult with a BMI below 18.5 is classified as underweight, a BMI ranging from 18.5 to 24.9 is considered within the healthy range, a BMI between 25 and 29.9 signifies overweight, and a BMI exceeding 30 indicates obesity. However, it's important to acknowledge individual variations before making definitive conclusions about the relationship between BMI and total body fat, as noted by Russell and Mueller. [31]

Electrolytes

Electrolytes are substances that, when dissolved in water, break down into ions carrying positive (cations) or negative (anions)

charges. They play a vital role in numerous metabolic processes, maintaining the body's physiological functions, including osmotic balance, acid-base equilibrium, and regulating intracellular and extracellular ion concentrations.

Calcium (Ca)

Although most the body's calcium (Ca++) is stored in the skeleton, the remaining 1% serves crucial physiological functions. Approximately half of the calcium found in the intravascular compartment binds to the whey protein albumin. Consequently, when serum albumin levels are low, total calcium levels decrease due to hypoalbuminemia.

In healthy adults, typical serum total calcium levels range from approximately 8.5 to 10.5 mg/dL, while normal ionized calcium levels range from 4.5 to 5.5 mEq/L. Changes in acid-base balance can inversely affect ionized calcium levels; an increase in whey pH causes calcium to bind to proteins, leading to decreased ionized calcium levels, whereas a decrease in pH has the opposite effect. Given calcium's critical roles in cardiac, nervous system, and musculoskeletal function, both hypocalcemia and hypercalcemia can pose life-threatening risks. Calcium levels are carefully regulated, with the actions of vitamin D and phosphorus playing significant roles. Vitamin D promotes calcium absorption in the GI tract, while phosphorus inhibits it.

In normal diet, dairy products serve as the primary source of calcium, along with some green vegetables, nuts, canned fish containing bones, and tofu enriched with calcium. Many food products are fortified with additional calcium by manufacturers. The recommended daily calcium intake varies from 1,000 to 1,300 mg, depending on age and gender, with an upper limit estimated at around 2,500 mg per day. [32]

Sodium (Na)

Serves as the primary cation within the extracellular fluid, playing a pivotal role in regulating extracellular volume and plasma. The normal serum concentration of sodium falls within the range of 136 to 145 mEq/L. Sodium also holds significance in neuromuscular function and the maintenance of acid-base balance. The preservation of serum sodium levels is of utmost importance, as severe hyponatremia can result in seizures, coma, and even fatalities. Contrary to common belief, sweat is hypotonic and contains relatively small quantities of sodium. The export of sodium from cells acts as the driving force for facilitating the transport of glucose, amino acids, and other nutrients into the cells.

The precise minimum dietary sodium requirements remain uncertain but are estimated to be quite low, at approximately 200 mg per day. The Dietary Reference Intakes (DRI) sets an upper limit of 2.3 grams of sodium daily or 5.8 grams of sodium chloride (common table salt) daily, considering the potential association of sodium with hypertension, as noted by Chobanian. [33] The primary source of sodium is sodium chloride, with approximately 40% of its weight comprising sodium. Protein-based foods naturally contain more sodium than vegetables and grains, while fruits contain minimal or negligible amounts of sodium. [32].

Magnesium (Mg)

The human body contains approximately 24 grams of magnesium, making it the second most abundant intracellular cation. Roughly half of the body's magnesium is stored in bone tissues, while another 45% is in soft tissues. Only 1% of the body's magnesium is found in the extracellular fluid. [34] Normal serum magnesium levels typically fall within the range of 1.7 to 2.5 mEq/L, with approximately 70% of serum magnesium existing in a free or ionized form, while the remainder is bound to proteins and remains inactive. Magnesium (Mg++) serves as a critical cofactor in numerous enzymatic reactions within the body. It plays a significant role in bone metabolism, as well as in the proper functioning of the central nervous system and cardiovascular system.

The consumption of magnesium and potassium, along with an increased intake of fruits and vegetables, has been linked to a more alkaline status, which has a beneficial impact on bone health. Consuming fortified mineral water can serve as a convenient and cost-effective method to reduce the risk of osteoporosis [35].

Magnesium is present in a wide variety of foods, making it unlikely for healthy individuals to experience isolated magnesium deficiencies. Highly processed foods generally contain lower levels of magnesium, whereas green leafy vegetables, legumes, and whole grains are rich sources. The recommended daily intake of magnesium varies between 310 to 420 mg, depending on age and gender [32].

Phosphorus (P)

Plays a crucial role in the intracellular fluid, and its contribution to adenosine triphosphate (ATP) is indispensable for energy metabolism. Additionally, phosphorus is vital in bone metabolism, with approximately 80% of the body's phosphorus content residing in the bones. Normal serum phosphorus levels typically fall within the range of 2.4 to 4.6 mg/dL. Due to its critical role in energy production, severe hypophosphatemia can pose a life-threatening situation.

Phosphorus is primarily present in animal-derived products such as meats and milk, while certain types of dried beans also serve as good sources. The recommended daily intake of phosphorus varies, approximately around 700 mg per day, depending on age and gender. There's an upper limit of 3,500 to 4,000 mg, as outlined by the Institute of Medicine [32].

Potassium (K)

Is the primary cation found within intracellular fluid, and present in smaller quantities in the extracellular fluid. Normal serum potassium levels typically range from 3.5 to 5.0 mEq/L. Potassium, in conjunction with sodium, plays a vital role in maintaining proper water balance, osmotic equilibrium, and acid-base balance. It is also essential, along with calcium, for regulating neuromuscular activity. Sodium and potassium concentrations are pivotal in determining membrane potentials in nerves and muscles.

Generally, potassium-rich foods include fruits, vegetables, fresh meat, and dairy products. The recommended daily potassium intake for adults is 4,700 mg/day, and no upper limit has been established. Inadequate potassium intake has been linked to conditions such as systemic arterial hypertension and cardiac arrhythmias, as indicated by the Institute of Medicine [32].

Bone Physiology

Bone tissue functions as a repository for calcium and various minerals required by other body tissues. Calcium homeostasis is the process of maintaining a consistent serum calcium concentration. In situations where the dietary intake is insufficient, the body heavily relies on this reservoir of calcium stored in bone tissue. Additionally, bone tissue is dynamic, undergoing continuous changes through a process of bone turnover, which includes modeling the skeleton during early growth and remodeling once skeletal development (height gain) is completed. Vitamin D collaborates with parathyroid hormone (PTH) to enhance the release of calcium from bone tissue, thus regulating blood calcium levels. Vitamin D primarily derives from the interaction between sunlight and skin precursors, and secondarily, from dietary sources [36].

When the resorption and formation phases are in balance, the amount of bone tissue at the end of the formation phase matches that at the start of the resorption phase. This remodeling process benefits the skeleton by renewing bone without causing microfractures. However, when dietary calcium intake is insufficient, osteoclastic resorption becomes relatively higher than osteoblast formation due to consistently elevated PTH levels in the bloodstream. This results in the removal of significant amounts of bone tissue that is not typically completely replaced [36].

Vitamins

Vitamins are essential micronutrients that play a crucial role in various biochemical processes within the body, including metabolism, immune function, and cell growth. They are vital for maintaining overall health and preventing deficiencies that can lead to a range of health issues, emphasizing their fundamental importance in supporting human well-being. Lower levels of vitamin C are related to higher analgesics consumption. [16] Vitamin D should be strongly assessed and supplemented since a high deficiency can be found globally. [5] Vitamin B12 is strongly associated with neurosensory disturbances recovery. [17,18] Vitamin A, iron, and generic supplements [12,13,19] also could be very useful in case of minerals/vitamins blood tests are not available.

CONCLUSION

In conclusion, while the realm of maxillofacial surgery sees significant advancements in virtual planning, emerging technologies, and pharmaceutical innovations, there exists a noticeable gap in addressing the nutritional status of surgical patients. This oversight can potentially lead to suboptimal postoperative outcomes. Recognizing the pivotal role of nutrition in enhancing surgical results, this paper emphasizes the importance of maintaining optimal nutritional status among orthognathic surgery patients. Additionally, a comprehensive perioperative nutritional protocol tailored to this patient population is proposed, aiming to reduce body weight loss post-surgery and improve bone formation. Constant research and updates in this domain are imperative for achieving further improvements in surgical outcomes.

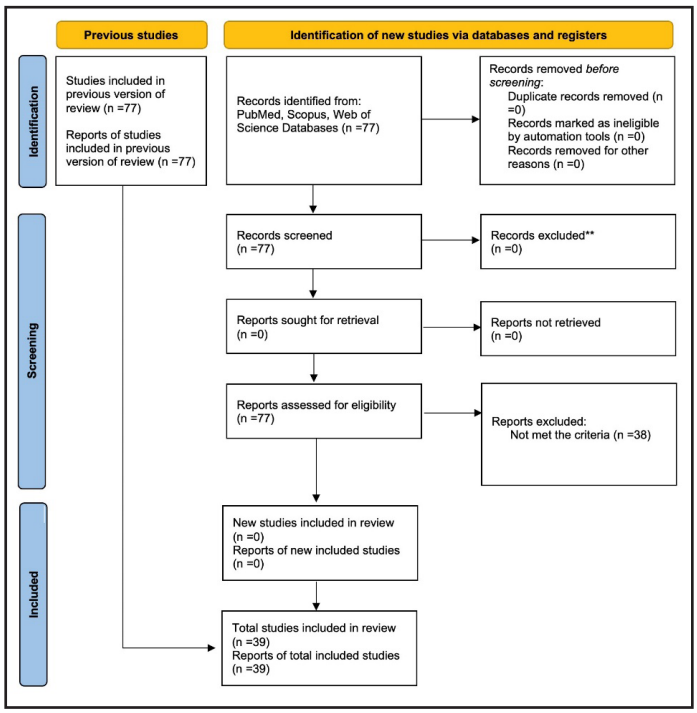

Figure 1. Flowchart of the included articles.

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

Funding: This article was not supported by any grant.

Authors Contribution: All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

During the preparation of this work the authors used ChatGPT in order to translate parts of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(3):409-418.
https://doi.org/10.58600/eurjther2148

Review Article

Factors Associated with Cytomegalovirus (CMV) Procto-Colitis in Immunocompetent Adults: A Systematic Review

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Received: 2024-04-17 **Accepted:** 2024-05-17 **Published Online:** 2024-05-17

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ABSTRACT

Objective: The pathophysiology of CMV procto-colitis in immunocompetent adults is poorly understood. We aimed to systematically review the literature to explore factors, presenting symptoms and endoscopy findings associated with CMV procto-colitis in immunocompetent adults.

Methods: Following PRISMA guidelines, we conducted a narrative systematic review by searching MEDLINE, EMBASE, EMCARE and CINAHL for manuscripts published up to August 2023. One author screened manuscript abstracts; two authors independently conducted a full text review. We included manuscripts which included primary data of immunocompetent adults with CMV procto-colitis except case reports. Quality and risk of bias was assessed independently by two authors using the Joanna Briggs institute critical appraisal tools.

Results: 8 manuscripts were included in the final review from the USA (n=2), China (n=2), Korea (n=2), India (n=1) and Brazil (n=1) and consisted of 6 case series, one case-control study and one cross-sectional study published between 1988-2022. We identified demographic and behavioural factors (older age, lower BMI, receptive anal sex), infection factors (urinary tract infections, shigellosis, Hepatitis C, COVID-19, sepsis, antimicrobial use), medical conditions (cardiovascular disease, respiratory disease, renal disease, auto-immune disease, diabetes) and hospitalisation factors (intensive care admission, longer length of hospital stay) associated with CMV procto-colitis in immunocompetent adults. Patients presented with rectal bleeding, diarrhoea, melaena, fever, nausea/vomiting, abdominal pain/bloating and constipation. Large bowel endoscopy findings were ulcers, erosions, and erythema and polyp/mass lesions.

Conclusion: We have highlighted factors, presenting symptoms and endoscopy findings associated with CMV procto-colitis in immunocompetent patients which provides insight for clinical guideline development and future research.

Keywords: Cytomegalovirus, CMV, Immunocompetent, non-immunocompromised, colitis, proctitis, gastrointestinal

INTRODUCTION

Cytomegalovirus (CMV) is a member of the herpes virus family which can cause a mononucleosis like-illness and has a high serology prevalence of 60-100% in most communities [1, 2]. Transmission occurs in a bimodal peak, the first peak in infancy likely related to placental transmission and horizontal spread amongst infants, and the second peak in young adulthood related to kissing and sexual transmission [3]. Following initial infection, CMV becomes latent and reactivation is well described in immunocompromised individuals such as those with advanced HIV infection, solid organ transplant, haematological and other malignancies, and undergoing chemotherapy and other immunosuppressants [3-8]. Reactivation can result in end organ disease including the retina, liver, lungs, central nervous system and gastrointestinal system [9]. Community seroprevalence indicates reactivation is usually the likely source of end-organ disease, although primary infection may contribute to a minority of cases [10].

Diagnosis of CMV procto-colitis is made by observation of viral inclusions on hematoxylin and eosin (H&E) staining of colonic/rectal mucosa histology, or immunohistochemistry staining. However H&E staining has a lower sensitivity (84%) and may be missed due to sampling error, for example due to a small histology specimen, while immunohistochemistry staining is the gold standard with higher sensitivity and specificity but requires clinicians to have a high degree of suspicion of CMV in order to request the appropriate investigation [11, 12]. Recent advances in PCR technology has made this available for the detection of CMV in histological samples however there is controversy about its use particularly regarding availability of fresh samples versus formalin-fixed, paraffin embedded tissue samples, and the potential for false-positive results given the high sensitivity and residual CMV DNA in tissue lymphocytes especially where there is inflammation [13].

Main Points:

We have explored and highlighted demographic and behavioural factors (older age, lower BMI, receptive anal sex), infection factors (urinary tract infections, shigellosis, Hepatitis C, COVID-19, sepsis, antimicrobial use), medical conditions (cardiovascular disease, respiratory disease, renal disease, auto-immune disease, diabetes) and hospitalisation factors (intensive care admission, longer length of hospital stay) and presenting symptoms and large bowel endoscopy findings associated with CMV procto-colitis in immunocompetent adults.

Severe manifestations of reactivated CMV in immunocompetent patients have been shown to be more common than previously believed, including the gastrointestinal tract (colitis), the central nervous system (meningitis, encephalitis, transverse myelitis), haematological disorders (haemolytic anaemia, thrombocytopenia, thrombosis of the venous or arterial vascular system), ocular involvement (uveitis), and lung disease (pneumonitis) [9]. CMV procto-colitis is well described in association with inflammatory bowel disease (IBD) [14]. Reactivation of CMV can be associated with flares in IBD, and is associated with older age, shorter IBD duration and pancolitis [14-16].

While CMV procto-colitis may be rare in immunocompetent adults, its sequelae can be severe requiring antiviral therapy and can be fatal [17]. The aim of this systematic review was to explore any factors including presenting symptoms and colonoscopy findings associated with CMV proctocolitis in immunocompetent adults to provide insights into the pathophysiology and inform future guidelines and research.

MATERIALS AND METHOD

Search Strategy and Selection

A systematic review of the literature was conducted in September 2023 using PRISMA guidelines to explore any factors associated with CMV in immunocompetent adults. We searched four bibliographic databases (MEDLINE, EMBASE and EMCARE via the Ovid interface; CINALH via the EBSCO host interface) to identify eligible manuscripts using the following search terms: (Cytomegalovirus OR CMV) AND (immunocompetent OR non-immunodeficient OR non-immunocompromised OR non-immunosuppressed OR nonimmunodeficient OR nonimmunocompromised OR nonimmunosuppressed) AND (proctitis OR colitis OR proctocolitis OR procto-colitis OR GI infection OR gastrointestinal). Manuscripts meeting the following criteria were included in our review: participants were immunocompetent, had a diagnosis of procto-colitis caused by CMV diagnosed using either immunohistochemistry staining or typical owl's eye and intracytoplasmic CMV inclusions on hematoxylin and eosin staining. We only included manuscripts written in English language, containing primary data where at least one variable (either observed or comparable) with Cytomegalovirus was explored and publication date was not

restricted. As we primarily wanted to explore factors associated with proctocolitis, we excluded manuscripts which reported the whole gastrointestinal tract where data on rectal infection could not be extracted separately, and participant populations under the age of 16. For the purposes of this study, we defined immune-suppressed as either living with HIV infection, solid organ transplant, haematological and other malignancies, and undergoing chemotherapy and other immunosuppressant or bone marrow suppressant therapy, or any genetic disorder causing immunosuppression. Where manuscripts contained mixed populations of immunocompetent and immunocompromised, we only extracted and analysed data from immunocompetent individuals. Manuscripts were excluded if the authors had included data on patients with solid organ transplants, haematological malignancies, on immunosuppressive therapy (such as chemotherapy), or were living with HIV. Manuscripts reporting on all other conditions were included. All types of study where primary data were reported were included except for case reports which were excluded due to their inherent bias and inherent inability to control for confounding factors. Conference abstracts, editorials, conference posters, review articles, opinion articles and grey literature were excluded due to their lack of peer review.

A staged process was used for screening and selection of manuscripts for the final review. Each record from the initial search of citations was imported into Rayyan software and duplicate citations were removed. Manuscripts abstracts were screened by the primary researcher (TB) and then full text manuscripts were then assessed for eligibility independently by the primary researcher (TB) and an associate researcher (KL). Any discrepancies were discussed (TB, KL and DR) for a final decision regarding eligibility.

Quality Assessment, Risk of Bias Assessment and Data Synthesis

Quality assessment and risk of bias was assessed for each manuscript independently by the primary researcher (TB) and the associate researcher (KL) using the Joanna Briggs Institute (JBI) critical appraisal checklists [18]. The final manuscripts were graded and marked either include, exclude or seek further information. Any discrepancies or manuscripts not reaching quality assessment threshold was discussed collectively (by TB, KL and DR) for a final decision. We synthesized and tabulated narrative data from the manuscripts. The review protocol was registered on PROSPERO (CRD42023455014).

RESULTS

The initial search identified 1001 citations, 336 duplicate citations were removed, 665 abstracts were screened for eligibility and 476 were excluded. We assessed 22 full text manuscripts for eligibility and 14 manuscripts were excluded. In total, 8 manuscripts were included in the final review [19-26] (Figure 1). Risk of bias was determined to be low in 4 manuscripts, moderate in 1 manuscript and high in 3 manuscripts. (Supplementary table 1) The manuscripts were from the USA (n=2), China (n=2), Korea (n=2), India (n=1) and Brazil (n=1) and included were 6 case series, one case control study and one cross sectional study published between 1988 and 2022 (Table 1). In total, there were 165 patients with CMV procto-colitis.

Demographic and Behavioural Factors

We found that CMV procto-colitis was associated with increasing age, lower body mass index and receptive anal intercourse [19, 24, 25] (Table 2).

Infection Factors

We found that infection (including urinary tract infection, shigellosis, hepatitis C, COVID-19, sepsis) and preceding anti-biotic use was associated with CMV procto-colitis [19, 21, 23, 24].

Medical Conditions

Our review has identified the following medical problems associated with CMV procto-colitis: cardiovascular (including coronary disease, cardiomyopathy, cerebrovascular disease and hypertension), respiratory disease (including pneumonia, COPD, pulmonary hypertension), renal disease (including acute/chronic renal impairment and dialysis), autoimmune disease (including rheumatological), sepsis and diabetes mellitus [19-26].

Symptoms

Patients with CMV procto-colitis presented with: rectal bleeding, diarrhoea and melaena, fever, nausea/vomiting, abdominal pain/bloating and constipation [19-26].

Colonoscopy Findings

Where lower bowel endoscopy was reported, patients with CMV procto-colitis were found to have: ulcers (including deep, superficial and serpiginous), erosions, erythema, colitis (including pseudomembranous) and mass-like lesions [19-22, 24, 26].

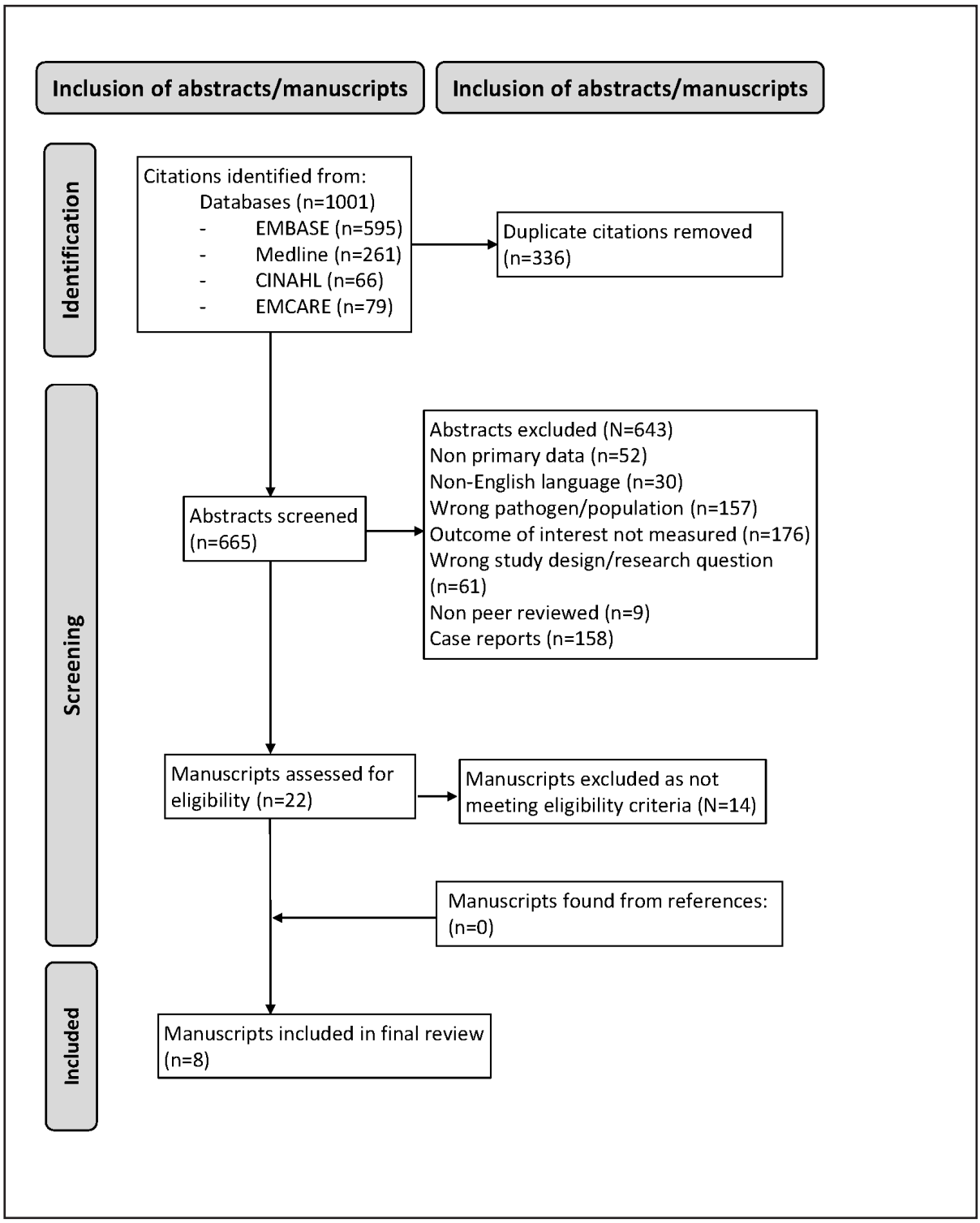

Figure 1. Flow chart of study selection for inclusion in the systematic review.

Table 1. Study design and risk factors associated with CMV procto-colitis in immunocompetent adults.

Manuscript	Study characteristics		Population	CMV testing	Factors associated with CMV in immunocompetent adults
Surawicz et al 1988, USA.[20]	Case series	Reported cases of CMV-procto-colitis	n=3 Aged 37 (female), 25 (male) and 71 (female)	Histology	**Behaviour:** receptive anal sexual intercourse Factors: erythema nodosum, urinary tract infection **Symptoms:** diarrhoea, rectal bleeding, constipation, fever **Endoscopy:** friable mucosa, mucosal erosion, serpiginous ulceration, cobble-stoning
Ng et al., 1999, China.[22]	Case series	CMV procto-colitis cases from 2 hospital pathology databases	n=10, Median age 70	Histology	**Factors:** *Shigella* dysentery, acute myocardial infarction, Psuedomonas/enterococcus pyelonephritis, gastric ulcer, HSV oesophagitis, cerebral infarction, hyperosmolar diabetic coma **Symptoms:** rectal bleeding, fever, diarrhoea, constipation **Endoscopy:** ulcers, erosion, polyp/growth, erythema
Klauber et al., 1998, USA.[21]	Case series	Reported cases of CMV procto-colitis	n=2 Aged 85 and 67 (male)	Histology	**Factors:** respiratory disease, sepsis **Symptoms:** diarrhoea, fever, rectal bleeding, abdominal pain, bloating **Endoscopy:** ulcer, erosions, erythema
Seo et al., 2012, Korea.[23]	Case series	Reported cases of CMV procto-colitis	n=12, Median age 66	Histology	**Factors:** diabetes mellitus, chronic renal failure, ischaemic heart disease. **Symptoms:** had GI bleeding, diarrhoea **Endoscopy:** ulcers
Siciliano et al., 2014, Brazil.[24]	Case series	Reported cases of CMV procto-colitis admitted to an intensive care unit	n=14, Median age 64	Histology	**Factors:** Hypertension, cardiomyopathy, congestive heart failure, pulmonary hypertension, chronic renal failure, diabetes mellitus, hepatitis C, autoimmune disease, chronic obstructive pulmonary disease, septic or cardiogenic shock, mechanical ventilation, vasoactive drugs, pneumonia, *Clostridium* colitis, acute renal injury, urinary tract infection **Symptoms:** rectal bleeding, diarrhoea, fever, nausea/vomiting, meleana, abdominal distension
Ko et al., 2015, Korea.[25]	Case control	Immunocompetent adults presenting with CMV procto-colitis and non CMV procto-colitis.	51 CMV-colitis patients, matched with 102 non-CMV-colitis. Mean age of cases =65 years	Histology & PCR	**Factors:** lower body mass index ($p=0.45$), requiring ICU care ($p<0.001$) renal disease ($p=0.037$), renal disease or hemodialysis ($p=0.003$), neurological disease ($p=0.013$), rheumatologic disease ($p=0.021$), antibiotic use ($p<0.01$), H2/PPI use ($p<0.001$). **Symptoms:** diarrhoea (45%), rectal bleeding (51%), fever (16%), abdominal pain (16%), melaena (8%), nausea/vomiting (6%) **Endoscopy:** ulcer (88%), erosion (37%), mass-like lesion (4%)

Le et al., 2017, Taiwan.[26]	Cross-sectional	immunocompetent and immunodeficiency cases of CMV procto-colitis from a pathology database.	69 CMV-colitis patients, 42 (61%) immunocompetent (mean age 64 years) and 27 (40%) immunocompromised	Histology	**Factors:** (compared with immunosuppressed patients with CMV colitis) age (older) (p=0.009), requiring ICU care (p=0.023), longer (days of) hospital stay (0.023), coronary artery disease (p=0.019), hypertension (p=0.01), **Symptoms:** melaena (52%), diarrhoea (36%), pain (29%), fever (41%).
Verma et al., 2022, India.[27]	Case series	Reported cases of CMV procto-colitis	n=4, Median age 54	Histology	**Factors:** diabetes mellitus, hypertension, COVID-19 **Symptoms:** diarrhoea (including bloody), abdominal pain **Endoscopy:** multiple ulcers (superficial and deep)

Table 2. Risk factors associated with CMV procto-colitis in immunocompetent adults

Demographic & behavioural factors	Older age Low body mass index Receptive anal sex
Infection factors	Urinary tract infection (including pyelonephritis) Shigellosis Hepatitis C COVID-19 Antimicrobial use Sepsis
Medical conditions	Cardiovascular (including coronary disease, cardiomyopathy, cerebrovascular disease and hypertension) Respiratory disease (including pneumonia, COPD, pulmonary hypertension) Renal disease (including acute/chronic renal impairment and dialysis) Autoimmune disease (including rheumatological) Diabetes Mellitus
Hospitalistation factors	Require intensive care unit admission Longer length of hospital stay (compared with immunosuppressed patients)
Presenting symptoms	Rectal bleeding Diarrhoea and melaena Fever Nausea/vomiting Abdominal pain/bloating Constipation
Endoscopy findings	Ulcer Erosion Erythema Polyp/mass

Hospitalisation Factors

We found that patients in our review with CMV procto-colitis frequently required intensive care unit admission and experienced longer length of stay in hospital (compared with immunosuppressed patients with CMV procto-colitis) [24, 25].

Although we were unable to estimate the pooled prevalence of factors in this review due to the nature of the manuscripts, broadly the prevalence of cardiovascular disease (excluding hypertension) was 22%, renal disease 28%, hypertension 29% and diabetes mellitus 28%. We were unable to establish the number of individuals with CMV proctocolitis in this review without risk factors.

DISCUSSION

Although it is well established that immunocompromised hosts can experience severe CMV disease including procto-colitis, the effects of CMV in immunocompetent patients is less understood. Characterizing the predisposing factors, presenting symptoms and endoscopic findings may improve the diagnosis, clinical guidelines and provide focus for future research. In this review, we have CMV procto-colitis in immunocompetent adults is associated with demographic and behavioural factors (including older age and lower BMI, receptive anal sexual intercourse), infection factors (including urinary tract infection, shigellosis, hepatitis C, COVID-19, sepsis and antibiotic use), medical conditions (including cardiovascular, respiratory, renal disease, autoimmune disease and diabetes) and hospitalisation factors (including requiring intensive care unit admission and increased hospital length of stay). We have also demonstrated that patients with CMV procto-colitis present with rectal bleeding, diarrhoea and melaena, fever, nausea/vomiting, abdominal pain/bloating and constipation. Colonoscopy findings describe ulcers, non-specific erosions, erythaema and polyp/mass like lesions.

We have shown that increasing age and having a low BMI is associated with CMV procto-colitis in immunocompetent adults: extremes of BMI and increasing age are well recognised to be associated with an increased risk of infection [27, 28]. It is interesting that immunocompetent individuals with CMV procto-colitis experience longer hospital length of stay and are more likely to require an ICU admission including compared with patients with immunodeficiency [24, 25]. There are several possible explanations for this including the presence of co-morbidity in immunocompetent people described in this review, compared to those with immunodeficiency, and selection bias for people with severe immunodeficiency where ICU may not be appropriate. This finding may also represent delays in diagnosis of CMV proctocolitis in immunocompetent patients. Sexual transmission of CMV is less well understood compared to other herpes viruses [29]. Although this review considers CMV procto-colitis to be a predominantly reactivation phenomenon, it may be that some cases are due to acute infection in the colon/rectum from sexual transmission. We were unable to explore this further in this review as no studies considered serological markers of CMV in their cases to delineate acute infection from reactivation. Mono and multiple infections of Herpes simplex viruses, *Treponema pallidum, Chlamydia trachomatis, Neisseria gonorrhoeae* and more recently Mpox are well described causes of an acute proctitis, mainly amongst men who have sex with men [30-32].

The colon is the most frequently affected end organ in CMV in immunocompetent adults and co-involvement with other organ systems (e.g. haematological) is rare [17]. The mortality of gastrointestinal CMV in immunocompetent adults is higher in those with diabetes and other medical conditions affecting immune responses (diabetes mellitus, renal disease, pregnancy and non haematological malignancy) [17]. TNF-α, IL-6 and INF-γ are increased in patients with acute and chronic inflammatory conditions for example: inflammatory bowel disease, renal disease, rheumatological disease, cardiovascular disease, respiratory disease, liver disease and infection including sepsis [33]. An increase in cytokines has been shown to promote the reactivation of CMV [17]. We suggest that the findings of this review provide further evidence that immunocompetent patients with acute or chronic inflammatory disease, including cardiovascular disease and renal disease are at risk of (reactivated) CMV procto-colitis.

Patients presenting with rectal and bowel symptoms including change of bowel habit, bleeding, unexplained diarrhoea, abdominal discomfort, and mass lesions require investigation for malignancy or inflammatory bowel disease. This review suggests that patients with the described risk factors of inflammatory disease should also be investigated for CMV procto-colitis even in the absence of immunodeficiency. In this review we have described the findings of lower bowel endoscopy namely ulcers, erosions, erythema, colitis and mass-like lesions which although may have a wide differential diagnosis, should further prompt clinicians to investigate CMV disease.

Limitations

There are several limitations to this review including having a small number of manuscripts and a small overall number of participants from mostly high-income settings. Although we decided a-priori to exclude case reports this review consisted of relative low-quality case series and a medium quality cross-sectional study and case control study making overall interpretation of the results challenging. There is likely to be significant reporting bias due to the complex nature of diagnostics required for CMV procto-colitis and many patients may experience missed opportunities for diagnosis. It is also likely that some important factors, presenting characteristics (including immunosuppressive states or treatment including corticosteroids) and endoscopic features were not reported accurately due to the nature of the manuscripts included in this review. This review focused on CMV procto-colitis, and manuscripts exploring CMV of the whole gastrointestinal tract where sufficient information about CMV procto-colitis could not be extracted were not included. Most manuscripts in this review used histology for the diagnosis of CMV procto-colitis (H&E staining or immunohistochemistry staining) which has limitations.

CONCLUSIONS

In summary, CMV procto-colitis presents some important diagnostic challenges and requires a high index of suspicion particularly in immunocompetent patients. Beyond traditional medical conditions known to cause immunodeficiency (e.g. advanced HIV), this review highlights the importance of considering pre-disposing pro-inflammatory medical conditions which may increase the susceptibility of immunocompetent patients to CMV disease and CMV procto-colitis. In any patient presenting with clinical deterioration and procto-colitis symptoms, it is important to ensure CMV is carefully considered during assessment. Further research exploring pro-inflammatory causes of reactivation of CMV in the rectum and colon of immunocompetent adults is needed.

Conflict of interest: non declared

Informed Consent: non required.

Funding: No funding

Ethical Approval: non required. Protocol registered on PROSPERO: (CRD42023455014).

Author Contributions: Conception: TB, DR - Design: TB, DR - Supervision: DR - Fundings: Nil - - Data Collection and/or Processing: TB, KL - Analysis and/or Interpretation: TB, DR Literature: TB, DR - Review: TB, KL, CF, DR - Writing: TB, KL, CF, DR - Critical Review: TB, KL, CF, DR

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How to Cite;

Bromley T, Lewis K, Fitzpatrick C, Richardson D (2024) Factors Associated with Cytomegalovirus (CMV) Procto-Colitis in Immunocompetent Adults: A Systematic Review. Eur J Ther. 30(3):409-418. https://doi.org/10.58600/eurjther2148

Supplementary material 1. Eligibility, quality and Risk of bias assessment

Authors	Year	Decision	Reason excluded	Risk of bias
Surawicz et al.	1988	Include		High
Cheung et al.	1993	Exclude	Case series of entire gastrointestinal tract	-
Klauber et al	1998	Include		High
Ng et al	1999	Include		Low
Crowley et al.	2002	Exclude	Case series included immunocompromised patients	-
Ng et al.	2003	Exclude	Case series included immunocompromised patients	-
Maiorana et al.	2003	Exclude	Case series of entire gastrointestinal tract	-
Chae et al	2010	Exclude	Case series of entire gastrointestinal tract	-
Agaimy et al	2011	Exclude	Case series included immunocompromised patients	-
Momin et al.	2011	Exclude	Case series where diagnosis was not confirmed with histology	-
Seo et al	2012	Include		Low
Siciliano et al.	2013	Include		Moderate
Ko et al.	2015	Include		Low
Ranjan et al	2015	Exclude	Case series included immunocompromised patients	-
Bernard et al.	2015	Exclude	Case series of entire gastrointestinal tract	-
Le et al.	2017	Include		Low
Kang et al	2018	Exclude	Cross sectional study of IBD patients	-
Chaemsupaphan et al.	2019	Exclude	Cohort study of entire gastrointestinal tract	-
Verma et al	2021	Include		High
Yoon et al.	2021	Exclude	Cross sectional study of entire gastrointestinal tract	-
Luangsirithanya et al.	2021	Exclude	Case series of entire gastrointestinal tract	-
Yeh et al.	2022	Exclude	Cross sectional study of entire gastrointestinal tract	-