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Letter to the Editor	500	No abstract	5	No tables	No media

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

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

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

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

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

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

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Contents

ORIGINAL RESEARCH ARTICLES

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Original Article

The Impact of First Year Clinical Variables of Heart Transplant Recipients on Ten-Year Survival

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ABSTRACT

Objective: Heart transplantation (HTx) is the treatment of choice for patients with end-stage heart failure. It is important to determine the factors related to long-term mortality at HTx. We aim to evaluate the effect of the first year clinical variables on 10-year survival at HTx.

Methods: The data of 76 consecutive adult HTx recipients who survived more than 1 year after transplantation between April 1998 and July 2007 in a tertiary medical center were retrospectively evaluated. The survival status was checked for each patient at December 2018. We analyzed the effect of renal function through creatinine levels, average resting heart rate, acute rejection episodes, infections, and left ventricular ejection fraction (LVEF) within the first year after HTx on survival.

Results: The mean age was 41 ± 12 years. Percentage of male was 84%. Median survival was 145 ± 32 months (95% CI, 80.72-209.27), and 36 out of 76 (47.3%) patients died during follow-up. LVEF was found lowered in nonsurvived group compared to survived ones [57.2 ± 5.8% vs 59.3 ± 2.1% ($P = .043$)]. Cox regression analyses revealed that only LVEF and creatinine at the end of the first year after HTx were found to be significantly associated with mortality [(HR = 0.91, 95% CI, 0.85-0.98, $P = .012$) and (HR = 1.09, 95% CI, 1.68-5.67, $P < .001$), respectively].

Conclusion: Decrease in LVEF and high serum creatinine level at the end of the first year after HTx were found to be associated with poor 10-year survival in HTx recipients.

Keywords: Heart transplantation, renal insufficiency, mortality

INTRODUCTION

Heart transplantation (HTx) is the gold standard treatment method that improves quality of life and survival of the patients with refractory heart failure since it was performed in 1967 by Christian Bernard in South Africa. Although the number of new adults on the waiting list shows an increase by almost 20%, the number of adult transplant (approximately 4,000 per year worldwide) has not increased over the last decade due to scarcity of donors.[1,2] Beside this, exceptional advances that have been achieved in immunosuppression, rejection control, and infection control have resulted in improvement in outcomes of HTx. However, it is important to determine the factors related to mid and long-term survival of HTx recipients despite the continuous improvements of survival particularly in the short-term over time. The mortality rate due to operation remains at 5-10%; on the other hand, first year survival rate reaches up to 85%, which decreases linearly by 3.4% per year. Infection, graft failure, and acute rejection are the most common causes of mortality within first year of transplantation. In the following years, cardiac allograft vasculopathy (CAV) and malignancy become the most common causes of death.[3] It is crucial to determine the factors related to mortality in terms of improving the mid- and long-term survival of adult HTx recipients especially in countries like ours, which have relatively limited number of HTx. In this regard, investigating some factors possibly related to mortality within the first year after HTx may provide an alerting data for long-term survival, so that necessary interventions can be made timely. Therefore, we aimed to evaluate the effect of some variables including renal function, resting heart rate, acute rejection episodes, infections, and left ventricular ejection fraction (LVEF) within the first year after HTx on mortality over a period more than 10 years in a cohort of HTx patients at our center.

METHODS

Patients at ages ranging from 18 to 70 who underwent HTx between April 1998 and July 2007 in Ege University Medical Faculty Hospital were retrospectively analysed, and each patient's survival status at least 10 years from transplantation was evaluated. Pediatric transplants, patients who died in the

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first year after transplantation, and who had pace maker were excluded from the study.

The study was conducted in accordance with the principles of the Declaration of Helsinki.

The data regarding patient's gender, age at transplantation, baseline heart rhythm and baseline medication after transplantation, preoperative diabetes mellitus, hypertension, hyperlipidemia history of recipients, donor age-gender, and etiology for transplantation were taken from patients' records. The reason for transplantation was classified into two groups as ischemic and nonischemic. Patients who had coronary artery disease were regarded as ischemic group. Nonischemic group composed of idiopathic cardiomyopathy, heart valve disease, congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and other etiologies. Similarly, according to patients' records, the cause of death was evaluated in five categories as cardiac, acute rejection, infection, malignancy, and unknown. Cardiac death was defined as sudden cardiac death (SCD) and fatal myocardial infarction.

The event was described as end of life due to one of the reasons mentioned earlier. The survival status of each patient who survived at least 1 year after HTx was checked in December 2018. The period of time from transplantation to the event was recorded as time to event in months. For patients who were alive at December 2018, time from transplant to December 2018 was calculated and recorded in months as well. None of the patients was dropped out as all follow-up data were available.

The heart rate was determined by analyzing the electrocardiograms or rhythm strip and recorded as beat per minute. The average values of heart rate at 1st, 6th, and 12th months were recorded as continuous variable. Renal function was estimated by serum creatinine levels, and ventricular dysfunction was defined as LVEF <50% with echocardiography; measurements of both serum creatinine and LVEF at the end of the first year after HTx were used in the study. Rejection episodes (ACR) were defined according to the standardized nomenclature of the International Society of Heart and Lung Transplantation (ISHLT).[4] Rejection episode was considered when a rejection was at a grade ≥2R with a significant need of increase in immunosuppressive or steroid treatment. CAV was considered when an intimal proliferation was ≥5 mm with the intravascular ultrasound in one or more epicardial coronary vessels. All variables and survival status were obtained from patient's archive files.

Main Points

- Mild decrease of left ventricular ejection fraction even within normal ranges in the first year post-heart transplantation might be associated with 10-year mortality.
- Increase in creatinine levels of heart transplant recipients in the first year after transplantation could be related with 10-year mortality.
- Median survival rate of heart transplant recipients was found at 12.0 years.

Variables were compared between patients who nonsurvived and survived during follow-up.

Statistical Analyses

Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPSS Corp.; Armonk, NY, USA) software was used for statistical analysis. Recipient age, donor age, ischemic time, creatinine levels, LVEF, and mean HR were compared between survived and nonsurvived patient groups by using Student t test. Chi-square was the choice of method to compare recipient gender, donor and recipient gender, the presence of ACR episodes, the presence of CMV and non-CMV infections, and the presence of CAV in the first year after transplantation, and the Fisher's exact test was used where Chi-square was not applicable. A value of $P < .05$ was assumed to be statistically significant. Additionally, Kaplan–Meier survival analysis was used to determine median survival time. Also, all factors possibly associated with survival were initially analyzed with Cox regression with enter method. A second Cox regression analysis with enter method was performed with variables that were found to be significant on survival in the first analysis.

RESULTS

Seventy-six patients were included in the analysis. All patients went through biatrial orthotopic HTx. The study population had a mean age of 41 ± 12 years. Percentage of male and female was accounted for 84 and 16, respectively. The most common reason for HTx was nonischemic etiology (76%). The median survival was 145 ± 32 months (95% CI, 80.72-209.27), and 36 out of 76 (47.3%) patients died during follow-up. The percentage of death causes was ordered from highest to lowest as follows: cardiac (n = 12, 33.3%), infection (n = 9, 25%), others (n = 6, 16.7%), malignancy (n = 5, 13.9%), and acute rejection (n = 4, 11.1%). The other characteristics of patients and their medications were given in Table 1.

We investigated the factors that may possibly affect mortality. Therefore, some variables, such as ACR episodes, mean heart rate, CMV infection, non-CMV infections within the first year following transplantation, CAV, recipient age–gender, donor age, donor–recipient gender mismatch, graft cold ischemic time, and also LVEF and creatinine levels at the end of the first year after HTx, were compared between patients who survived and nonsurvived during follow-up. Among these variables, LVEF was found mildly lowered in nonsurvived group compared to survived ones [57.2 ± 5.8% vs 59.3 ± 2.1% ($P = .043$)]. Although creatinine levels of patients who died were higher than those of patients who survived, the difference was not statistically significant, but P value was close to significance [1.42 ± 0.95 mg dL^{-1} vs 1.11 ± 0.30 mg dL^{-1} ($P = .074$)] (Table 2). Additionally, only three patients in the nonsurvived group have required hemodialysis at the end of the first year. None of the patients in the survived group required hemodialysis. Furthermore, we used a multivariable Cox regression analysis to determine the effects of possible factors considered to be related to mortality in heart transplant patients. In the first analysis, all factors were assessed, and a negative association of LVEF and a positive association of creatinine level with mortality were found [(HR 0.90, 95% CI, 0.83-0.97, $P = .012$) and (HR 2.54, 95% CI, 1.05-6.16, $P = .038$), respectively]. In the second

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Survived (n = 40)	Nonsurvived (n = 36)
Age at HTx (years)	40.02 ± 12.82	42.94 ± 11.20
Men [n (%)]	35 (87.5)	29 (80.5)
Mean survival time (months)	163.82 ± 31.90	71.13 ± 52.41
BMI (kg m^{-2})	22.92 ± 3.65	23.22 ± 3.02
DM [n (%)]	1 (2.5)	3 (8.3)
Hypertension [n (%)]	2 (5.0)	0 (0)
Hyperlipidemia [n (%)]	5 (12.5)	2 (5.6)
Preop LVAD [n (%)]	4 (10.0)	0 (0)
Reason for HTx [n (%)]		
Ischemic [n (%)]	11 (27.5)	7 (19.4)
Nonischemic [n (%)]	29 (72.5)	29 (80.5)
Baseline Medications [n (%)]		
Steroids [n (%)]	40 (100)	36 (100)
Induction therapy [n (%)]	2 (5.0)	3 (8.3)
Cyclosporine [n (%)]	33 (82.5)	26 (72.2)
Azathioprine [n (%)]	9 (22.5)	10 (27.8)
Tacrolimus [n (%)]	12 (30.0)	12 (33.3)
Sirolimus [n (%)]	1 (2.5)	2 (5.6)
Everolimus [n (%)]	4 (10.0)	0 (0)
Mycophenolate mofetil [n (%)]	31 (77.5)	26 (72.2)
ß blockers [n (%)]	0 (0)	1 (2.8)
Verapamil [n (%)]	5 (12.5)	1 (2.8)
Diltiazem [n (%)]	11 (27.5)	7 (19.4)
ACEI/ARB [n (%)]	17 (42.5)	14 (38.9)
Diuretic [n (%)]	20 (50.0)	13 (36.1)
Donor Characteristics		
Donor age (years)	28.02 ± 8.96	30.94 ± 11.31
Donor gender [(male) %]	35 (87.5)	32 (88.9)
Female donor/male recipient [(n %)]	2 (5.0)	2 (5.5)
Male donor/female recipient [(n %)]	2 (5.0)	5 (13.8)
Cold ischemic time (minutes)	178.61 ± 54.14	158.30 ± 52.87
Cause of Death		
Cardiac [n (%)]	N/A	12 (33.3%)
Acute rejection [n (%)]	N/A	4 (11.1%)

Table 1. (Continued)

Variable	Survived (n = 40)	Nonsurvived (n = 36)
Infection [n (%)]	N/A	9 (25%)
Malignancy [n (%)]	N/A	5 (13.9%)
Other [n (%)]	N/A	6 (16.7%)

Abbreviations: BMI, body mass index; DM, diabetes mellitus; LVAD, left ventricular assist device; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; N/A, not applicable.

Table 2. Comparison of Assessed Possible Risk Factors Related to Mortality Between Survived and Nonsurvived Groups in Study Population

Variables	Survived (n = 40)	Nonsurvived (n = 36)	*P*
Recipient age (years)	40.02 ± 12.82	42.94 ± 11.20	.293
Recipient gender (male, %)	87.5	80.6	.303
Donor age (years)	28.26 ± 8.96	30.94 ± 11.31	.228
Male donor/male recipient [n (%)]	33 (55.0)	27 (45.0)	.246
Male donor/female recipient [n (%)]	2 (28.6)	5 (71.4)	
Female donor/male recipient [n (%)]	2 (50.0)	2 (50.0)	1.000
Female donor/female recipient [n (%)]	3 (60.0)	2 (40.0)	
Ischemic time (minutes)	178.61 ± 54.14	158.30 ± 52.87	.105
ACR episode in first year (%)	20.0	22.2	.517
Creatinine in first year (mg dL^{-1})	1.11 ± 0.30	1.42 ± 0.95	.074
LVEF in first year (%)	59.38 ± 2.14	57.23 ± 5.85	.043
Mean heart rate in first year (bpm)	98.98 ± 9.81	97.30 ± 15.25	.565
CMV infection (%)	52.5	36.1	.114
Non-CMV infections (%)	22.5	36.1	.146
CAV in first year (%)	2.5	9.4	.228

Abbreviations: ACR, acute cellular rejection; LVEF, left ventricular ejection fraction; CMV, cytomegalo virus; CAV, cardiac allograft vasculopathy.

analysis, only these two variables were analyzed using Cox regression with enter method, and their significance was remained for mortality [(HR 0.91, 95% CI, 0.85-0.98, $P = .012$) and (HR 1.09, 95% CI, 1.68-5.67, $P < .001$), respectively] (Tables 3 and 4).

DISCUSSION

HTx is the treatment of choice for patients with end-stage heart failure. According to ISHLT 2017, median survival is 10.7 years for adult HTx patients. In our study, median survival was slightly higher at 12.0 years.

Looking at the factors related to mortality, LVEF and serum creatinine level at the end of the first year after HTx showed an association with long-term survival in this study. LVEF was found mildly lowered in nonsurvived group compared with survived ones [57.2 ± 5.8% vs 59.3 ± 2.1%, $P = .043$], and also it was detected significantly associated with mortality in final regression analysis (HR 0.91, 95% CI, 0.85-0.98, $P = .012$). Left ventricular systolic function that is commonly assessed by echocardiographic LVEF usually shows lower values in clinically stable HTx patients compared with healthy subjects.[5] It is a well-established method of short- and long-time evaluation of

Table 3. Initial Multivariate Analysis of Possible Risk Factors Related to Mortality

Variable	B	HR	*P*	95% CI
Recipient age	0.00	1.00	.779	0.96–1.04
Recipient gender	–0.57	0.56	.247	0.21–1.48
Donor age	0.02	1.02	.367	0.97–1.06
Ischemic time	0.00	1.00	.922	0.99–1.00
ACR episode	0.11	1.12	.821	0.40–3.13
Creatinine level	0.93	2.54	.038	1.05–6.16
LVEF	–0.10	0.90	.012	0.83–0.97
Mean heart rate	0.00	1.00	.985	0.96–1.04
CMV infection	–0.22	0.79	.618	0.33–1.93
Non-CMV infections	0.60	1.82	.202	0.72–4.61
CAV in rst year	0.80	2.23	.267	0.54–9.20

Abbreviations: ACR, acute cellular rejection; LVEF, left ventricular ejection fraction; CMV, cytomegalo virus; CAV, cardiac allograft vasculopathy; HR, hazard ratio.

Table 4. Second Multivariate Analysis of Possible Risk Factors Related to Mortality

Variable	B	HR	*P*	95% CI
Creatinine level	1.12	3.09	<.001	1.68–5.67
LVEF	–0.08	0.91	.012	0.85–0.98

Abbreviation: LVEF, left ventricular ejection fraction; HR, hazard ratio.

graft condition and an important predictor of outcomes in heart transplant.[6] Barbir et al.[7] showed that LVEF >60% was significantly able to predict survival without myocardial infarction and/or heart failure and/or and also was able to predict cardiac death in HTx patients. Additionally, the study of Vakil et al.[8] revealed that the percentage of SCD accounted for approximately 10% among all deaths after HTx, and LVEF ≤40% was the important predictor of SCD in adult HTx patients. However, some limitations regarding LVEF should be noted. LVEF is a volume-based echocardiographic parameter providing an indirect assessment of myocardial function. Although it is an important predictor of outcomes in various cardiac disease including heart transplant patients, it could be in normal ranges even in patients with early systolic dysfunction detected by global longitudinal strain measurements.[9–11] On the other hand, LVEF measurements have an interobserver variability relating to LV cavity border tracing and geometric assumptions.[12] Therefore, these factors should be considered when interpreting our results, which showed LVEF was in normal ranges and there was a small difference between groups.

ISHLT registry has revealed that renal failure is one of the leading causes of death among HTx patients, especially in long term. Approximately 25% of HTx patients showed elevated serum creatinine levels at the end of the first year post-HTx, 51% at 5-year post-HTx, and 68.4% at 10-year.[13] Post-transplant renal failure has been mostly attributed to calcineurin inhibitors that are used for immunosuppression. On the other hand, several other non-immunosuppression-related factors such as recipient age, female gender, diabetes, hypertension, hepatitis C infection, and impaired renal and postoperative acute renal failures have been found to contribute to impaired kidney function during the first year after HTx.[14,15] We found that creatinine levels of patients who died were higher than those of patients who survived. Although the difference was not statistically significant in univariate analysis, *P* value was close to significance [1.42 ± 0.95 mg dL^{-1} vs 1.11 ± 0.30 mg dL^{-1}, $P = .074$]. However, Cox regression analysis revealed that creatinine level at first year after HTx was associated with increased risk of mortality (HR 1.09, 95% CI, 1.68-5.67, $P < .001$). The significant association between renal failure after HTx and mortality and morbidity has been previously reported.[16–19] Arora et al.[20] have shown that the significant number of HTx recipients demonstrated a decrease by 25 mL/min/1.73 m^2 at glomerular filtration rate (GFR) within the first year after HTx, and this decline of GFR was associated with a higher risk of both all cause and cardiac mortality. Also, GFR at first year (<60 mL/min/1.73 m^2) post-HTx was found to be capable of predicting 5, 10, and 15-year all-cause and cardiac mortality. Additionally, Navarro-Manchon et al.[21] concluded that although GFR shows rapid reduction in the first few months, it might be a reliable indicator of renal reserve as it stabilizes at the end of first year after HTx and shows slow, continuous deterioration. Furthermore, only severe renal dysfunction at first year was found to be an independent predictor of all-cause mortality among various

factors in HTx patients. GFR is usually a preferred method for the assessment of renal function in HTx patients because of fluctuations can be seen in creatinine levels due to a number of factors. On the other hand, it has been shown that GFR calculated by the abbreviated MDRD (Modification of Diet in Renal Disease) equation is no superior to serum creatinine at first year after HTx in terms of predicting long-term mortality.[22] Therefore, we thought that creatinine level at the end of first year after HTx could be a reliable marker to define renal reserve. In this regard, as it was reported that renal protective approaches probably could be effective at early phases of renal damage.[23]

We found that mean first year heart rate was similar between groups and did not affect survival in HTx patients. Denervation of the donor heart during HTx, which causes loss of parasympathetic and sympathetic regulation, results in increased resting heart rate and also loss of expected rapid heart rate response to exercise.[24] The studies regarding heart rate and survival after HTx reported that higher heart rates within the first year after HTx could be related to cardiovascular and all-cause mortality.[25–28] Nonetheless, the relation between increased heart rate and poor prognosis has not been fully understood yet. It is not clear whether tachycardia is simply an outcome of clinical status or it is a cause of worsening prognosis on its own. From another point of view, increased heart rate could be a compensatory response to underlying conditions such as hypovolemia, anemia, graft dysfunction, bronchopulmonary disease, or infection.[29,30]

Regarding the other factors that were investigated in our study, ACR episodes, infections, and CAV seen within first year after HTx were not found to be related to long-term mortality. Infection and acute rejection are among the most commonly reported causes of mortality particularly within first year of transplantation[13]; therefore, our findings could be expected as patients who died within first year after HTx were not included in this study. With respect to CAV which is one of the common causes of death after transplantation, it is usually seen in the following years rather than in the first year after transplantation.[13] Therefore, the reason why we could not find a relation between CAV and mortality could be related to the design of our study investigating variables including CAV only in the first year after transplantation.

There are some worth mentioning limitations of our study. This study reflects the data of a single center. The retrospective design and relatively small number of patients are other limitations of this study. As it is known, the retrospective collection of data may cause data inaccuracy, lack of information, and patient selection bias in comparison to prospectively acquired data. Also, including large number of variables in the logistic regression model with a relatively small number of patients in the study cohort may have a potential risk for statistical anomaly. Nevertheless, we managed to gather a comprehensive database, and our analysis has revealed several important findings related to post-HTx mortality within 10 years.

CONCLUSION

This study demonstrated that even small decrease in LVEF and increase in serum creatinine level at the end of the first year after HTx might be associated with poor long-term survival in heart transplant recipients. Therefore, these parameters need to be checked carefully and monitored particularly within the first year after transplantation as they can potentially affect the long-term outcome of HTx.

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Original Article

The Effect of Acromiohumeral Distance on Isolated Supraspinatus Tendon Tear Repair

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ABSTRACT

Objective: The aim of this study is to evaluate whether preoperative acromiohumeral distance has any prognostic value in predicting postoperative functional outcomes after repair of isolated supraspinatus tear.

Methods: Patients who underwent arthroscopic supraspinatus tear repair between 2015 and 2019 were evaluated retrospectively. Magnetic resonance imaging (MRI) and arthroscopic findings of tears were classified according to Patte classification; patients in group II, segment III in the sagittal plane, levels 1 and 2 in the frontal plane, biceps tendon intact, and without acromioplasty were included in this study. Group I consisted of 63 patients (F = 38; M = 25) with the tear at the insertion level and group II with 41 patients (F = 23; M = 18) with the stump at the level of the caput humeri. Preoperative and postoperative radiographs and MRI were compared by measuring the acromiohumeral distances of the patients. Patients were evaluated functionally with the use of American Shoulder and elbow surgeon shoulder score and Constant-Murley score.

Results: There was no significant difference between the two groups in terms of age, gender, and the affected side. Jobe and drop sign test results were significantly positive in group II. There was no significant difference between the two groups in terms of functional scores, preoperatively and postoperatively. There was a statistically significant improvement in group I in postoperative abduction, flexion, and external rotation movements in terms of joint range of motion. In radiological evaluation, there was a statistically significant difference in all measurements in group I compared to group II.

Conclusion: The preoperative acromiohumeral distance has no prognostic value in predicting postoperative functional outcomes.

Keywords: Acromiohumeral distance, arthroscopic repair, shoulder, supraspinatus tear

INTRODUCTION

The rotator cuff (RC) muscles protect the glenohumeral joint by providing the axial compressive force required for the contact of the humeral head with the glenoid joint face.[1] In RC tears, with the disappearance of compressive force, the deltoid muscle becomes the main force that pulls the humeral head upwards.[2] Golding,[3] in their study of 150 asymptomatic people, suggested that acromiohumeral distance (AHD) may vary between 6 and 14 mm. It has been stated that AHD smaller than 6-7 mm is associated with RC tears, and values below 6 mm are a reliable radiological finding of massive RC tears that cannot be successfully repaired.[2–5]

Hamada et al.[6] were the first author to describe the progression of radiological findings of massive RC tears. In RC rupture, it has been stated that the deltoid muscle contracts with the flexion movement and the humeral head migrates proximally, thus causing a decrease in AHD. In the advanced stage, they suggested that the force transferred to the long head of the biceps by suppressing the humeral head down increased, and the mechanical friction seen between the humeral head and the lower surface of the acromion could tear the long head of the biceps tendon and narrow the AHD further.[6] This explains the more frequent rupture of the supraspinatus tendon.[7]

There are studies in the literature on the effect of posterior and posterosuperior localized infraspinatus tendon ruptures on AHD.[8–11] There are debates on the importance of isolated supraspinatus rupture in AHD. With this study, we aim to evaluate whether preoperative AHD has any prognostic value in predicting postoperative functional outcomes after repair of isolated supraspinatus tears.

METHODS

This study was prospectively registered to ethical board of The Gaziosmanpasa University Medical Faculty approval and grant number of the study is 20-KAEK-278. In our study, patients who underwent arthroscopic supraspinatus tendon tear repair between 2015 and 2019 were evaluated retrospectively. Exclusion criteria: <35 and >75 years of age, follow-up for less than 12 months, history of rheumatologic and neurological diseases, the previous shoulder joint infection, fracture or surgery in the shoulder area, pseudoparalysis, acromion pathology, and biceps pathology with grade 3 or higher glenohumeral

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Table 1. Patte Classication

Extend of tear	Group I: partial tears and full-thickness tears <1 cm in sagittal diameter;
	A: deep partial tears
	B: supercial tears
	C: small full substance tear
	Group II: full substance tears of entire supraspinatus
	Group III: full substance tears involving more than one tendon
	Group IV: massive tears with secondary osteoarthritis
Topography of tear in sagittal plane	Segment 1: subscapularis tear
	Segment 2: coracohumeral ligament tear
	Segment 3: isolated supraspinatus tear
	Segment 4: entire supraspinatus and half of infraspinatus tear
	Segment 5: entire supraspinatus and infraspinatus tear
	Segment 6: subscapularis, supraspinatus and infraspinatus tear
Topography of tear in frontal plane	Stage 1: proximal stump close to bony insertion
	Stage 2: proximal stump at level of humeral head
	Stage 3: proximal stump at level of glenoid
Quality of muscle	1. Minimal fatty layer
	2. Fatty tissue less than muscle tissue
	3. Fatty tissue is equal to muscle tissue
	4. Fatty tissue more than muscle tissue
State of long head of biceps	1. Intact
	2. Subluxation
	3. Dislocation

arthrosis according to Hamada classification.[6,12] Magnetic resonance imaging (MRI) and arthroscopic findings of tears were classified according to Patte classification[13] (Table 1). Patients with the degree of a tear in group II, segment III in the sagittal plane, levels 1 and 2 in the frontal plane, intact biceps tendon, and without acromioplasty have been filtered from records and surgery notes. One hundred and fifty-eight patients meeting the current criteria were identified, and 104 patients who came for the last control were included in this study.

Main Points

- It was determined that as the degree of supraspinatus tear increased, preoperative physical examination findings and symptoms were more severe, but preoperative functional life scores did not differ.
- Postoperatively, improvement in AHD did not affect functional scores in all patients, but the only improvement was in joint ROM.
- The preoperative AHD has no prognostic value in predicting postoperative functional results in isolated supraspinatus tendon tears.

Functional Evaluation

Preoperative, American Shoulder and elbow surgeon shoulder score (ASES), and Constant-Murley scores (CMS) of the patients filtered from archives were evaluated and compared with their functional scores in the last follow-up. Along with this, physical examination tests, Jobe and drop sign that are the specific to the supraspinatus tendon, were evaluated in the preoperative and final control examinations.

Radiological Evaluation

In our clinic, true anterior–posterior (AP) radiography and MRI are routinely performed preoperatively in each patient operated for RC tear. In this study, patients were evaluated radiologically by having an MRI with true AP radiography at the last control. AHD was measured and compared on preoperative

Figure 1. AHD measurement on X-ray.

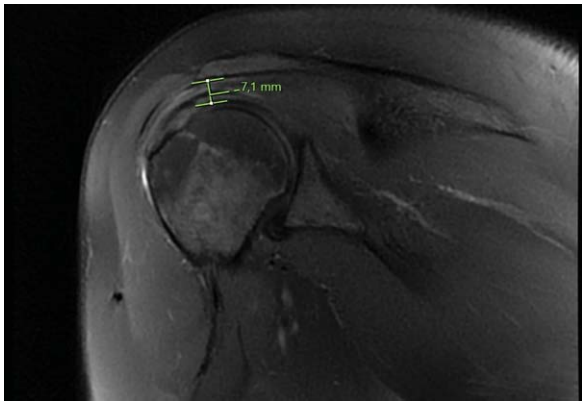
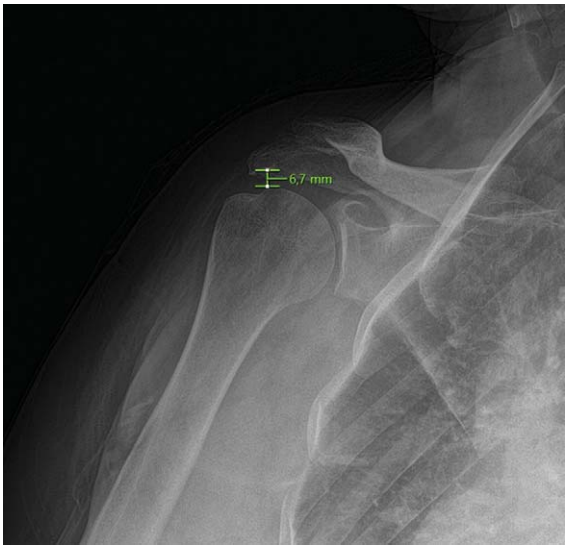


Figure 2. AHD measurement on MRI.



and postoperative radiographs and MRI. Radiographic measurements were made between the sclerotic cortical bone on the inferior face of the acromion and the most proximal narrow distance of the humeral head parallel to this line[14] (Figure 1). The reliability and accuracy of the measurement of AHD have been made according to the studies in the literature.[5,14,15] MRI was performed using a device with a 1.5 T magnetic field strength (MAGNETOM Avanto, Siemens Medical Solutions, Erlangen, Germany). These shots were made with the patient lying in the supine position, the arm in a neutral position in adduction and the forearm in pronation. AHD measurements in MRI were made by measuring the shortest distance between the top of the humeral head and the acromion in sagittal sections synchronized with T1-weighted coronal section (Figure 2). All radiological evaluations were measured separately by two observers, and average of both values was recorded.

Statistical Analysis

The data obtained were evaluated using Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Corp.; Armonk, NY, USA) program. Normally distributed data were presented as mean ± SD, and data not normally distributed as median (IQR). The distribution of data was evaluated using Kolmogorov–Smirnov test. Student-t-test was used for normally distributed data, and Mann–Whitney U test was used for non-normally distributed data. Repeated-ANOVA and Wilcoxon's test were used to evaluate dependent groups. Chi-square test was used to evaluate categorical variables. A *P*-value of $<.05$ was considered significant in all tests.

RESULTS

The mean age was 56 years (range 41-65). Sixty-one patients were female (F) and 43 patients were male (M). Seventy-nine patients were operated on the right shoulder and 25 patients on the left shoulder. The dominant extremity was in the right side in 88 patients and in the left side in 16 patients. The average follow-up period is 28 months (19.2-34).

Preoperatively, 64.4% of the patients were positive for the Jobe test and 40.4% for the drop sign test, and all patients had a complete improvement in these tests postoperatively. Preoperative and postoperative range of motion (ROMs) of the patients are given in Table 2.

Table 2. Comparison of Preoperative and Postoperative Range of Motion

	Preoperative	Postoperative	*P*
Abduction	100° (90–120)	150° (140–160)	<.001
Flexion	140° (120–160)	160° (160–170)	<.001
Extension	45° (35–50)	50° (45–60)	<.001
Internal rotation	L4 (L5–L1)	L1 (L3–L1)	<.001
External rotation	30° (20–33.7)	40° (30–45)	<.001

Median (IQR) values are presented.
P < .05 values were considered significant.

Table 3. Comparison of the Effects of Supraspinatus Tendon Tear Level on Clinical Outcomes According to Patte Classication Frontal Plane Topography

		Group I (n = 63)	Group II (n = 41)	*P*
Age		55.25 ± 7.38	56.97 ± 5.05	.195
Gender	Female	38 (60.4%)	23 (56.1%)	.689
	Male	25 (39.6%)	18 (43.9%)	
Affected side	Right	46 (73.1%)	33 (99.4%)	.384
	Left	17 (26.9%)	8 (0.6%)	
Jobe test	Positive	33 (52.4%)	34 (82.9%)	.001*
	Negative	30 (47.6%)	7 (17.1%)	
Drop sign test	Positive	23 (36.6%)	22 (53.7%)	.026*
	Negative	40 (63.4%)	19 (46.3%)	
Preoperative Constant–Murley score		49 (41–52)	50 (42–56)	.155
Postoperative Constant–Murley score		87 (84–90)	84 (83–87)	.122
Preoperative ASES		45.55 ± 5.1	45.17 ± 3.8	.683
Postoperative ASES		86 (84–88)	84 (83–87)	.311
Preoperative abduction		100 (90–120)	100 (90–115)	.389
Preoperative exion		140 (130–160)	150 (120–160)	.659
Preoperative extension		45 (35–50)	45 (35–50)	.826
Preoperative internal rotation		L4 (L5–L3)	L4 (L5–L1)	.125
Preoperative external rotation		30 (30–30)	30 (20–35)	.882
Postoperative abduction		150 (150–170)	150 (140–160)	.005*
Postoperative exion		160 (160–180)	160 (160–165)	.032*
Postoperative extension		50 (45–60)	50 (45–55)	.110
Postoperative internal rotation		L1 (L2–L1)	L2 (L3–L2)	.053
Postoperative external rotation		50 (45–60)	50 (45–55)	<.001*

Mean ± SD and median (IQR) values are presented.
*$P < .05$ values were considered significant.

The average AHD value in the radiograms was 7.61 ± 0.7 mm for preoperative and 9.7 mm (9.1-10) for postoperative. Average AHD value in MRI examinations was 6.6 ± 0.6 mm for preoperative and 8.51 ± 0.5 mm for postoperative. Overall, a statistically significant difference was found between radiography ($P < .001$) and MRI ($P < .001$) in terms of preoperative and postoperative AHD values. The preoperative CMS was 50 (range: 42-56), and postoperative CMS was 86 (range: 84-90). The preoperative mean ASES score of the patients was 45.4 ± 4.6, and the postoperative ASES score was 86 (84-88). There was a significant improvement in all functional scores compared to preoperation (CMS, $P < .001$; ASES, $P < .001$).

Patients were divided into two groups according to the Patte classification of frontal plan topography in terms of localization of the torn stump. Group I consisted of 63 patients with insertion level (F = 38; M = 25) and group II of 41 patients (F = 23; M = 18) with stump at the level of the caput humeri. There was no significant difference between the two groups in terms of age, gender, and the affected side. Jobe and drop sign tests were significantly positive in group II. There was no significant difference between the two groups in terms of functional scores, preoperatively and postoperatively. In terms of ROM, all movements in group I have a greater range of motion than group II. There was a statistically significant improvement in group I especially in postoperative abduction, flexion, and external rotation movements (Table 3).

Table 4. Comparison of the Effects of the Supraspinatus Tendon Tear Level on the Radiological Results According to Patte Classication Frontal Plane Topography

	Group I (n = 63)	Group II (n = 41)	*P*
Preoperative AHM (X-ray)	7.98 ± 0.60	7.04 ± 0.67	<.001
Postoperative AHM (X-ray)	9.8 (9.3–10.1)	9.1 (9.0–9.7)	<.001
Preoperative AHM (MRG)	6.87 ± 0.56	6.15 ± 0.55	<.001
Postoperative AHM (MRG)	8.65 ± 0.55	8.31 ± 0.51	.003

Mean ± SD and median (IQR) values are presented.
$P < .05$ values were considered significant.

In radiological evaluation, there was a statistically significant difference in all measurements in group I compared with group II (Table 4).

DISCUSSION

Our study shows successful clinical and functional results of isolated supraspinatus tears repaired arthroscopically and their positive reflections on radiological results. It is a study in which diagnostic arthroscopic findings and MRI were evaluated together and other joint pathologies were eliminated, and patients with isolated supraspinatus tendon ruptures were evaluated.

Compared with a glenoid centered humeral head, the proximally migrated humeral head has been associated with lower ASES, CMS, restricted ROM, and lower patient satisfaction.[16–18] In recent studies about imaging methods to evaluate the displacement of the humeral head in RC tears, they evaluated the benefits of parameters such as upward migration index (UMI), inferior glenohumeral distance (IGHD), acromial index, and critical shoulder angle (CSA) other than AHD.[19–22] On the other hand, the literature regarding the clinical use of parameters such as UMI, IGHD, and CSA is not clear, AHD is still accepted as a prognostic indicator that affects functional outcome.[22]

Measurement of AHD with MRI is seen as a more practical and accurate method than X-ray. Kim et al.[19] showed that AHD measured on MRI is an independent predictor. The AHD limit value measured in MRI was accepted as ≤6 mm.[14] AHD measured by MRI is smaller than AHD measured by X-ray. MRI is performed when lying down, while the X-ray is performed when standing, and this AHD difference occurs because of gravital pull.[14,22] While MRI eliminates the position variable with standard patient positioning, it allows the distances between bony landmarks to be evaluated accurately. The radiographic mark defining the lower edge of the acromion in X-ray is a sclerotic line tangent to its lower surface. Since this line is not a fixed anatomical landmark, its location can change with changes in the direction of the X-ray. There is no such disadvantage for MRI. Werner et al.[14] found the inter method correlation coefficient r = 0.6 (moderately high) for AHD measured on X-ray and MRI. In our study, similar results were obtained between the measurements of preoperative and postoperative mean AHD by X-ray and MRI by the literature. Also, following the lower level of supraspinatus tear in group I, AHD improved postoperatively more significantly in both X-ray and MRI compared with group II.

Proximal migration of the humerus is more significant in symptomatic RC tears than in asymptomatic.[11] Correct clinical examination of the shoulder plays a crucial role in the diagnosis of RC tears. Pain, weakness, limited ROM, and various clinical tests are used for the clinical evaluation of the supraspinatus tendon. Moreover, this symptom and the ability of clinical tests to distinguish between complete and partial tears are unclear.[23,24] In a study using diagnostic arthroscopy findings, it was reported that many specific tests were unable to distinguish between partial and full-thickness tears of the supraspinatus tendon, and a combination of at least three tests was necessary for a correct diagnosis.[25] In our study, it was observed that the pain level was higher in group II (according to the pain criteria in CMS), and specific tests such as Jobe and drop sign were found to be more positive. At the same time, it was observed that preoperative AHD measurements were narrower in group II radiologically.

It has been reported that tears extending to the infraspinatus tendon are more symptomatic and associated with more proximal migration.[8–11] Weiner and Macnab[2] identified the supraspinatus tendon as the force depressing the humeral head. They stated that there is a balance between the deltoid muscle and the supraspinatus in the proximal humerus.[2] They suggested that if the supraspinatus tendon is torn, this balance is disturbed and the proximal pulling force of the deltoid muscle migrates the humeral head proximally.[2] de Oliveira França et al.[26] reported that in the frontal plane topography according to Patte classification, as the degree of tear retraction increases, AHD becomes narrower. A threshold of migration has been established in symptomatic shoulders relative to the area of the tear.[11] A tear area of 175 mm^2 fits a full-thickness tear, in which the supraspinatus tendon is slightly retracted (1 cm). Tears with an area of >175 mm^2 cause more proximal migration than smaller tears.[11] As in our study, according to the Patte classification frontal plan topography, it is clearly explained that why AHD is narrower than grade I in grade II tears. It was determined that as the degree of supraspinatus tear increased, preoperative physical examination findings and symptoms were more severe, but functional life scores did not differ significantly.

The biceps tendon has long been acting as a dynamic depressor for the humeral head.[27,28] For this reason, we decided to exclude patients with biceps tendon pathologies that play an active role in the task of depressing the humeral head in shoulders with RC tears, and patients who underwent surgery for the biceps tendon may directly affect AHD in our study.

In our study, no statistically significant difference was found between the groups in terms of preoperative overall ROM. However, postoperative shoulder abduction, flexion, and external rotation movements were found to be enormously superior to group II in group I. Extension and internal rotation, in accordance with the literature, were not significantly affected in both groups preoperatively and postoperatively.[29,30]

Our study has some limitations such as being a retrospective study and having a small sample size. Measurement bias may occur as only two orthopedic surgeons who make all measurements. Also, proximal migration was evaluated with only one parameter, AHD.

CONCLUSION

In isolated supraspinatus tears, it was observed that AHD had no effect on preoperative symptoms, ROM, and functional life scores. Postoperatively, improvement in AHD did not affect functional scores in all patients, but the only improvement was in joint ROM. It is evident that as the tear level increases following the tear level, the AHD will narrow.

As a result, the preoperative AHD has no prognostic value in predicting postoperative functional results in isolated supraspinatus tendon tears.

Ethics Committee Approval: Ethical committee approval was received from the Clinical Research Ethics Committee (20-KAEK-106).

Informed Consent: Written consent was obtained from the patients for before the surgery and postoperative final medical examination.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.O., F.E.; Design - T.O., F.E.; Supervision - T.O., F.E.; Materials - T.O., F.E.; Data Collection and/or Processing - T.O., F.E.; Analysis and/or Interpretation - T.O., F.E.; Literature Search - T.O.; Writing Manuscript - T.O., F.E.; Critical Review - T.O., F.E.

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Original Article

The Immediate Effects of Muscle Energy Technique on Range of Motion and Isokinetic Muscle Strength in Volleyball Players with Glenohumeral Internal Rotation Deficit: A Randomized Controlled Trial*

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ABSTRACT

Objective: The purpose of the present study was to investigate acute effects of muscle energy technique (MET) for the posterior shoulder on glenohumeral joint (GHJ) range of motion (ROM) and isokinetic peak torque values of GHJ rotators.

Methods: Eighteen male volleyball players volunteered to participate. All participants attended both MET trial for the GHJ horizontal abductors and sham trial. Preintervention and postintervention internal rotation (IR) and external rotation ROM and GHJ rotators isokinetic peak torque values were measured. Repeated measures one-way ANOVA and Bonferroni correction were used for analyzing the differences in the ROM and isokinetic parameters among the trials. Significance was defined as $P \leq .05$.

Results: The experimental group had a significantly greater increase in GHJ IR ROM postintervention compared to the control group ($P = .005$). No significant difference between the experimental group and control group was found for external rotation ROM ($P > .05$). However, a significant increase between the control/experimental and sham trials was found for external rotation ROM postintervention ($P = .005$). Besides, 60° internal rotator ($P = .001$) and external rotator ($P = .008$), and 180° internal rotator ($P = .019$) and external rotator ($P = .049$) peak torque values showed significant increase between the experimental and control/sham trials.

Conclusion: A single application of an MET for the posterior shoulder provides immediate improvement in GHJ IR ROM and isokinetic peak torque values of both GHJ internal and external rotators in asymptomatic volleyball players.

Keywords: Volleyball, muscle strength, shoulder joint

INTRODUCTION

Volleyball is a highly technical sport in which exceptional velocities and extreme forces repetitively generated. An elite volleyball player may perform as many as 40,000 volleyball attacks (spike) a year, which belongs to overhead/throwing motion. In a spike performance, velocities and forces produced by the arm transmitted to the ball while the maximum level of accuracy maintained simultaneously. This is performed by initially abducting and externally rotating the dominant arm at maximal positions, following adducting and internally rotating it rapidly.[1,2] This demanding high technical movement may result in shoulder injuries as well as various adaptations of the hitting shoulder as described in the relevant literature.[2–4]

Specifically, as described in the majority of the studies, the dominant shoulder may demonstrate external rotation gain, increase in external rotation range of motion (ROM) and GHJ internal rotation deficit (GIRD) (decrease in internal rotation (IR) ROM), muscular imbalance mainly due to the increased strength of IR with unchanged or lower external rotation (ER)

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strength, which have been linked with morphological shoulder adaptations and consequently shoulder pathology.[5–7] Posterior capsule tightening from repetitive microtrauma during throwing phases and posterior shoulder muscle tightness secondary to increased deceleration forces of the arm after throwing phases are the most common causes for those adaptations.[8,9] As a result, the length–tension relationship of the muscles involved in throwing such as internal and external rotators may be manifested through changes in capsular tightness and decreased ROMs.[10] It was confirmed that the altered length–-tension relationship of the muscle fibers could limit the maximum force-producing capacity of the muscle.[11]

There are several treatment approaches for GIRD in the literature particularly related to stretching intervention with conflicting results.[10–14] One of these approaches is the muscle energy technique (MET), which is time and cost-effective in the clinical settings.

MET is a relatively new manual therapy technique with just a few published studies.[15–17] The technique has been used to increase the flexibility[16] and ROM of a restricted joint.[15] During MET, the patient creates a force by activating the targeting musculotendinous unit against an accurately directed counterforce applied by the physiotherapist, and then a passive stretch applied by a physiotherapist following relaxation.[16] Mainly, two underlying mechanisms are expressed for treating a specific muscle. The reciprocal inhibition reflex is assumed to occur to inhibit antagonist muscle during contraction of agonist muscle to perform a smooth motion. Following repetitive isotonic contractions agonist progressive resistance could increase muscle tone and performance. Afferents from both Golgi tendon organs and gamma afferents from muscle spindle feedback to the medulla spinalis. Efferents from medulla spinalis with a new information return to the intrafusal fibers to resetting their new resting length and weak muscle tone can be increased by both repetitive isometric contractions and optimum length–tension relationship.[18]

Therefore, we hypothesized that the MET application would improve in glenohumeral internal rotation deficit of the shoulder and performance of the rotator muscles of athletes playing volleyball regularly. The purpose of the current study was to investigate the immediate effects of the MET on ROM of IR and isokinetic performance of rotator muscles in volleyball players with GIRD.

Main Points

- Immediately after muscle energy technique (MET) application, internal rotation range of motion of shoulder would improve in volleyball players with glenohumeral internal rotation deficit.
- MET application had an immediately positive impact on shoulder rotator muscles isokinetic strength.
- Optimizing muscle length–tension relationship using MET application could improve contraction capacity of muscle, which results in higher isokinetic muscle strength production.

Table 1. Demographics of the Participants (n = 18)

	Mean	Standard Deviation
Age (year)	20.39	2.25
Weight (kg)	79.61	11.97
Height (m)	1.87	0.08
BMI (kg m^{-2})	22.74	2.88
Adduction right (°)	35.28	8.24
Adduction left (°)	32.17	7.37
ROM right IR (°)	52.44	10.86
ROM right ER (°)	99.22	8.30
ROM left IR (°)	68.39	9.97
ROM left ER (°)	95.11	7.78
60° peak torque IR (Nm)	43.11	7.93
60° peak torque ER (Nm)	33.44	6.45
180° peak torque IR (Nm)	31.50	4.63
180° peak torque ER (Nm)	25.22	4.77

Abbreviations: BMI, body mass index; ROM, range of motion; IR, internal rotation; ER, external rotation.

METHODS

Participants

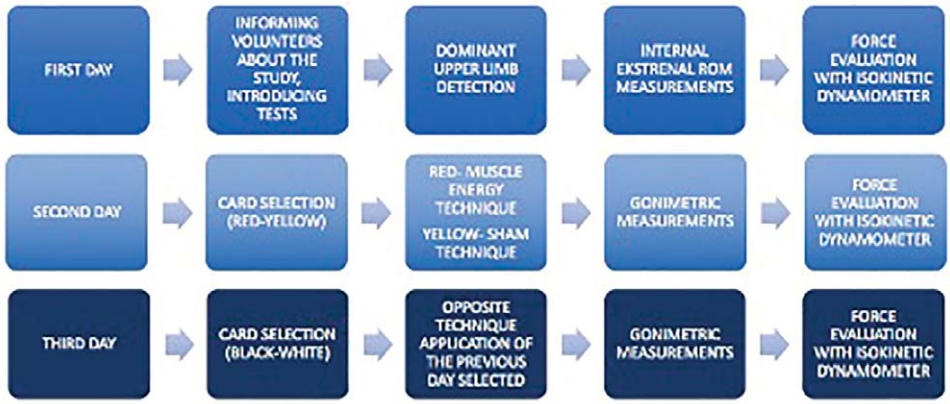
Thirty-six volleyball players participated in the current study voluntarily. All participants had been playing volleyball for 1-4 years. Their weekly program included an amateur match and three training sessions lasting for at least 2 hours on alternate days. Table 1 demonstrated the demographic information of the participants. Exclusion criteria were as follows: having any abnormality in body biomechanics, any shoulder injury in the last 6 months, any shoulder surgery history, any systemic pathology observed in the last 3 months, corticosteroid injection in any glenohumeral joint (GHJ) in the last 3 months, and lack of active joint motion deficit of dominant side GHJ.

Procedure

This study was carried out in the performance laboratory. All participants were informed about the procedure of the study, and an informed consent was obtained from all volunteers. This study was approved by the ethical committee (approval no: 2017/384).

The participants who met with inclusion criteria were recruited for further assessments of the study. Twenty-one of the 36 volleyball players had GIRD on their dominant extremity according to goniometric measurements. GIRD was defined as a difference in active IR ROM more than 18° between dominant and

Figure 1. The description of the randomization.



nondominant sides.[19] Nondominant IR ROM of the participants was found to be within the normal ranges as described in the previous literature.[20]

Participants were performed isokinetic muscle testing (Cybex HUMAC 2015; v.9.7.1; CSMI Solutions) for their dominant internal and external rotators (data obtained at the baseline measurements were determined as control). On the following day, participants were invited for interventions. Three of them did not attend, and 18 of the volunteers were included in the current study. The methodology of the study was planned as a randomized controlled double-blind.

Although all participants had planned to have both intervention methods during the study, they were asked to select one of the yellow and red cards to determine which intervention to undergone first and second days. The red card represented the MET, while the yellow card indicated the sham application.

MET application (experimental) to dominant side GHJ horizontal abductors and sham application performed by a physiotherapist-1 (PT). Immediately after that, the dominant side active IR and ER ROM values of the participants' joints were measured using the goniometer by the PT2. Later on, IR and ER muscle peak torque testing was performed using the isokinetic dynamometer and recorded in a computer by the PT2.

In the next study day, the participants were asked to choose the card again. However, second applications were selected regardless of the chosen card, and the color of the cards was changed to black and white to prevent the bias. Second-day applications for each participant were determined according to their previous applications; thus, the participants had MET application before changed to sham for the second application. On these processes, the participants and PT2 had no information about what the cards mean. The description of the randomization was presented in Figure 1.

Isokinetic Dynamometer Tests: The dynamometer was calibrated before the start of the study according to the operating manual. During all tests, participants were directed verbally, and visual feedback from the computer screen was not allowed to prevent the participant's psychological impact. The testing procedure was mentioned previously. Before measurements, athletes performed 5 minutes warm-up protocol in self-selected velocity by using hand dynamometer. After that, the participants were positioned on supine laying down position on the dynamometer, and dominant side GHJ and elbow joint were positioned in 90° of abduction and 90° forearm flexion, respectively. The dynamometer's rotational axis was aligned with the GHJ's axis. Velcro straps were fastened across the abdomen and chest to facilitate the activation of muscles, which affect the ROM and measurements, during exercise. To avoid excessive extension and flexion, the maximal ROM was set with safety stops from the center of the dynamometer's axis of rotation. To optimize muscle performance, the lengths of the forearm and control shaft were adjusted. According to the literature, concentric shoulder rotation was performed with five repetitions at an angular velocity of 60° s^{-1} and 15 repetitions at 180° s^{-1}. There was a 30-second break between sets.[21] Before all measurements, two trials for each condition were performed for familiarization with the protocol. No gravity correction was used for all tests.

Sham Protocol: The sham protocol replicated the treatment condition with the therapist-positioned athletes arm in 90° shoulder flexion and with the elbow flexed. The athlete was asked to perform an isometric contraction with minimum effort in the same position. After the contraction, the athlete asked to abduct his harm. The participant was then instructed to relax. The number of sets and time intervals were similar to MET application.

Muscle Energy Technique: MET was applied to the dominant side GHJ horizontal abductors. The applications were performed in the supine position. The PT1 stabilized the scapula at the lateral border and with the elbow flexed. The shoulder was horizontally adducted to the first barrier of motion, and the participant was asked to perform a 5-second isometric contraction at approximately 25% maximal effort in the direction of

Table 2. Repeated Measures One-Way ANOVA Analysis Results of Measured Values

					95% CI			
		Mean	SD	SE	L. Bound	U. Bound	f	*P*
ROM IR (°)	Control	52.44	10.86	2.56	47.05	57.84	8.004	.005
	Sham	53.61	9.46	2.23	48.91	60.31		
	Experimental	58.67[a]	12.89	3.04	52.26	65.08		
ROM ER (°)	Control	99.22[b]	8.30	1.96	95.10	103.35	8.017	.005
	Sham	97.56	7.48	1.76	93.84	101.27		
	Experimental	99.17[b]	8.35	1.97	95.02	103.32		
60° peak torque IR (Nm)	Control	43.11[b]	7.93	1.87	39.17	47.05	22.326	.001
	Sham	40.22	9.94	2.34	35.28	45.16		
	Experimental	47.56[c]	9.51	2.24	42.83	52.29		
60° peak torque ER (Nm)	Control	33.44	6.45	1.52	30.24	36.65	5.585	.008
	Sham	33.83	6.71	1.58	30.49	37.17		
	Experimental	36.83[c]	7.32	1.73	33.19	40.47		
180° peak torque IR (Nm)	Control	31.50	4.63	1.09	29.20	33.80	4.452	.019
	Sham	29.67	7.41	1.75	25.98	33.35		
	Experimental	34.11[c]	6.80	1.60	30.73	37.49		
180° peak torque ER (Nm)	Control	25.22	4.77	1.13	22.85	27.60	3.201	.049
	Sham	24.06	5.00	1.18	21.57	26.54		
	Experimental	27.61[b]	8.10	1.91	23.59	31.64		

Abbreviations: SD, standard deviation; SE, standard error; CI, confidence interval; IR, internal rotation; ER, external rotation, ROM, range of motion.
[a]Significant difference from control trial.
[b]Significant difference from sham trial.
[c]Significant difference from experimental trial.

horizontal abduction, against a resistance provided by the PT1 at the distal humerus. Perform a 5-second isometric contraction at approximately 25% maximal effort in the direction of horizontal abduction, against an opposing force provided by the examiner at the distal humerus. After the contraction, the participant was asked to pull his arm across his body, as the physiotherapist applied a 30 second active-assisted stretch. Later on, relaxation was instructed, and a new movement barrier was detected by the PT1. The protocol was repeated three times.[16]

Statistical Analysis

The statistician was blinded to group assignments. Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) program was used for statistical analyses. The data were expressed as the mean, standard deviation, standard error, and confidence intervals. The Shapiro–Wilk test was used for assessing normality. Repeated measures one-way ANOVA and Bonferroni correction were used for analyzing the differences in the ROM and isokinetic parameters among the trials. Significance was defined as $P \leq .05$.

RESULTS

Table 2 shows the differences between the control, sham, and experimental trials. In the IR ROM measurement, there was a significant increase between the experimental and control trials ($P < .05$). The significant increment was found between the control/experimental and sham trials of external rotation ROM ($P < .05$).

Besides, 60° internal and external rotation and 180° IR peak torque values showed a significant increase between the experimental and control/sham trials ($P < .05$). Also, 180° external rotation peak torque value showed a significant difference between the experimental and sham trials ($P < .05$). Figure 2 shows the control, sham, and experimental trials' values of external and IR ROM measures.

Figure 2.. The control, sham, and experimental trials' values of external and internal rotation range of motion measures.

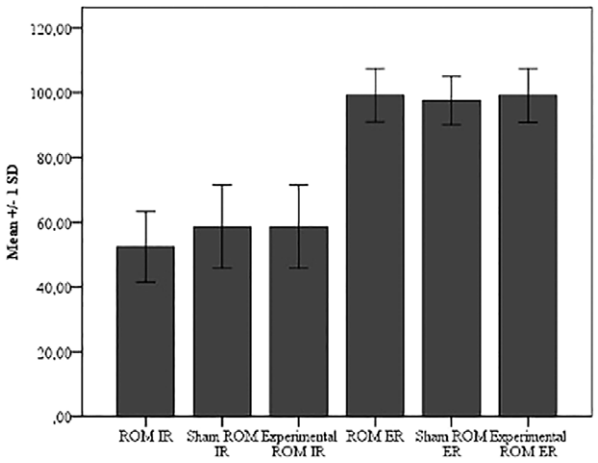
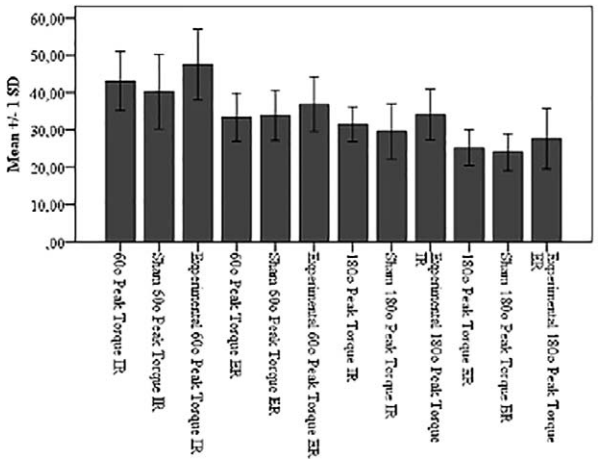


Figure 3.. The control, sham, and experimental trials' external and internal rotation isokinetic peak torque values.



The experimental trials had a significantly greater increase in GHJ IR ROM postintervention compared to control trials ($P = .005$). No significant difference among experimental trials and control trials were found for external rotation ROM ($P > .05$). The significant increase between the control/experimental and sham trials was found for external rotation ROM postintervention ($P = .005$). 60° internal rotator ($P = .001$) and external rotator ($P = .008$), and 180° internal rotator ($P = .019$) and external rotator ($P = .049$) peak torque values showed significant increase between the experimental and control/sham trials. Figure 3 shows the control, sham, and experimental trials' external and IR isokinetic peak torque values.

DISCUSSION

The results of our study confirmed our hypothesis that immediately after MET application, IR ROM of the shoulder and isokinetic rotator muscle performance would improve in volleyball players with GIRD.

The previous study including athletes with GIRD reported that MET application on horizontal abductors resulted in greater IR ROM, while MET for external rotators did not show any difference than the control group.[22] That is why in the current study only horizontal abductors were selected to apply MET to improve ROM of internal rotators. By improving ROM, it was considered that it would be possible to generate greater muscle activation leading to greater muscle strength.[23]

Several studies have investigated stretching of shoulder joint especially the posterior part, which includes tight posterior capsule in individuals with GIRD as a part of the treatment program. However, most of them used different types of stretching such as passive stretch,[10] sleeper stretch,[8] cross-body stretch,[13] etc. and reported conflicting results. Also, one of the previous studies indicated the improvement in IR ROM at least within 2 weeks.[12] Most of them used this technique during weekly rehabilitation programs. The immediate effect of stretching on ROM is still unclear. On the other hand, our results indicated that MET could improve immediately after the application ROM of IR in the shoulder with GIRD. It may be speculated that the acute effects of any intervention have significant importance for athletes during training and match periods.

Another important factor for an athlete is to achieve maximum performance during functional movements. Isokinetic muscle strength is one of the indicators of muscle performance.[24] In the current study, MET application had a positive impact immediately on rotator muscle isokinetic strength. Unfortunately, we did not include any performance assessments in our study design to make a clear conclusion about improvement in performance.

A study that was conducted to determine whether MET provides improvements in resting pectoralis minor muscle length, forward scapular position, and scapular upward rotation in female collegiate swimmers founded that the MET application increases pectoralis minor muscle length, and the result of that decrease, scapular forward position.[13] This biomechanical positional correction could result in an optimum length–tension relationship of a muscle. In line with this result, MET application in our study could lead to proper shoulder position, which was related to increased IR ROM and isokinetic rotator muscle strength.

On the other hand, ER ROM values of participants reduced after all applications, but unexpectedly, there was much more decrease after the sham application than MET application. The measurements were made while the season was in progress, and there was no extensive time to do the measurement. Because of that, we applied the testing procedure day by day and assessments lasted 3 days. Due to randomization, the number of participants involved in the sham application may have the majority on the last day of the study. In other words, people who involved the sham application may have already involved the MET application, and its effects may continue.

Although some studies involved MET application on cervical, thoracic, and lumbar spine,[13,16,25,26] application on shoulder

joint is lacking. Furthermore, only two studies are investigating the effectiveness of MET application on individuals with GIRD.[16,27] One of these studies performed a randomized controlled trial in 30 athletes and indicated that MET on the shoulder was an effective approach through regaining IR ROM in this population parallel with the results of the current study.

As mentioned previously, one of the limiting factor force production capacity of muscle could be related to its impaired length–tension relationship due to GIRD. Optimizing the length–tension relationship using MET could improve contraction capacity of muscle, which results in higher isokinetic strength production. One of the possible explanations for improvement in rotator muscle isokinetic strength after MET application in the current study could be related to optimizing the length–tension relationship as discussed.

Up to our knowledge, this study is one of the first that investigate the immediate effect of MET application in volleyball players with GIRD through shoulder ROM and rotator muscles isokinetic strength.

The measurements were made while the season was in progress. Therefore, we could not include long-term results of MET application on assessed parameters in the study design. This situation is the limitation of our research. In the future research, the long-term effects of MET application on shoulder ROM and muscle strength could be investigated.

CONCLUSION

Little is known about the immediate effects of MET application on shoulder ROM and muscle performance in volleyball players with GIRD. The results of the study might provide some new insight into the interventions used to treat negative motor outcomes of GIRD in volleyball players who need the optimum performance of shoulder muscles, especially rotators, during training and matches.

Ethics Committee Approval: Ethical committee approval was received from the Gaziantep University (approval no: 2017/384).

Informed Consent: Verbal informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.E.E., S.Z., A.B., Ö.M., A.Ö.; Design - A.E.E., S.Z., A.B., Ö.M.; Supervision - S.Z., A.Ö., Ö.M.; Resources - S.Z., A.Ö.; Materials - A.E.E., A.B., Ö.M., A.Ö.; Data Collection and/or Processing - A.E.E., A.B., Ö.M.; Analysis and/or Interpretation - A.E.E., Ö.M.; Literature Search - A.Ö.; Writing Manuscript - A.E.E., A.B.; Critical Review - A.E.E., S.Z., A.B., Ö.M., A.Ö.

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Original Article

Comparison of Urine Culture and Flow Cytometric Methods for Detecting Bacteriuria by Using a Simulation Model

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ABSTRACT

Objective: We aimed to simulate and assess a new screening model to determine and exclude culture negative urine samples before culturing for patients with preliminary diagnosis of urinary tract infections (UTIs). This prospective and single-center research included a simulation model that studied in a central laboratory between March and April 2020. All samples studied fluorescent flow cytometry (FC) analyzer and then inoculated to medium.

Methods: Simulations of infected urine were created by mixing certain amounts microorganisms with the urine. Standard *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans* strains, one *Lactobacillus* spp., and one *Staphylococcus epidermidis* clinical isolate were used in the study. After the dilution process, 42 infected urine samples were analyzed using UF5000i FC device and urine culture method. Correlation between the methods (culture and FC) for bacterial counts was assessed with the in-class correlation coefficient and Spearman correlation coefficient.

Results: A significant agreement was observed between the methods only for the urine dilution containing 10^5 CFU mL^{-1} pathogen.

Conclusion: The flow cytometric system failed to predict bacteriuria and the risk of urinary tract infection in our simulation model. Further research in combination with other parameters is needed to see the real power of flow cytometric methods for screening UTIs.

Keywords: Urinary tract infections, urine culture, flow cytometric method, simulation model

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common infections in patients attending hospitals and healthcare settings. These types of infections generally respond rapid to antibiotic treatment; as a result, it is important to rapidly diagnose and treat these infections.[1] The gold standard for etiologic diagnosis of UTIs is urine cultures; however, it generally takes 48 hours to perform urine culture and then microbiological identification of bacteria.[1–4] The isolated pathogen then has antibiogram performed after culture processes to ensure the clinician begins the patient on an appropriate antibiotic.[1] Urine samples are one of the most commonly used samples in clinical laboratories, and more than half of cultures provide negative results.[5] As a result, screening methods identifying and excluding clinically insignificant bacteriuria gain importance for urine samples.[6] There are many screening tests used to research the presence of bacteria and/or leukocytes in urine for UTI diagnosis. The most commonly used tests are gram staining of urine, nitrite test for enteric bacilli, leukocyte count in urine, and the identification of pyuria with leukocyte esterase activity.[1,2] In recent years, cytometric methods have come to the fore for UTI screening with the development of flow cell count devices. Flow cytometry (FC) method ensures differentiation of bacteria, leukocytes, erythrocytes, and other particles in urine. The Sysmex UF-5000i (Sysmex Corporation, Japan) is an automated latest generation FC device that has a second channel that may identify bacteria, and this device is proposed to have high sensitivity and specificity.[7] The FC UF-5000 analyzer used in our study was produced as a third generation fully automatic urine device. This analyzer may differentiate 17 diagnostic cell parameters and perform cell counts; additionally, the integrated body fluids (BFs) mode may classify and count seven diagnostic parameters. The system uses fluorescent FC technology at 480 nm wavelength and can perform two different analyses with a semiconductor laser and hydrodynamic focusing of surface (SFch) and core (CRch) analyses. Particles are stained with specific fluorochromes for both nucleic acid and surface in the device and sent into the laser. Counts and classifications are determined according to the emerging signals. These signals are, in order, signals from forward scattered light (FSC), side scattered light (SSC), side fluorescent light (SFL), and the new depolarized side scattered light (DSS). Specific algorithms analyze these light signals, and particles are differentiated into categories as identified. Due to different stain intake into the cell wall structure, FSC, SFL, and SSH light signals are used to differentiate gram-negative and

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gram-positive bacteria. Based on this, the UF-5000 system is reported to be able to image gram morphology of bacteria, and this situation is described as Bact Info flag in the device.[8] When the UF series is compared with older versions, the sensitivity and specificity features for bacterial identification have been enhanced with technological innovations. Additionally, the UF-5000 is better for fungal detection.[9] Though devices performing cytometric counts are reliable and can provide rapid results, fragmented leukocytes and dead bacteria affect the sensitivity of the test. Additionally, as noninfectious inflammation causes may create pyuria, leading to similar symptoms, urine culture is definitely necessary for these types of patients.[1] Etiologic bacterial UTI diagnosis is made with urine culture.[10] After incubation of noninvasive urine culture samples (midflow urine or Foley catheter), observation of $\geq 10^4$ CFU mL^{-1} colony counts on media or $\geq 10^3$ CFU uropathogen mL^{-1} for women from 14 to 30 years is accepted as significant for UTI.[2] The gold standard for UTIs is to take a urine culture before beginning antibiotic treatment.[2,3]

In this study, we aimed to simulate and assess a new screening model to determine and exclude culture negative urine samples before culturing for patients with preliminary diagnosis of UTI by clinicians. Preconditions for our screening model were high sensitivity of the screening test to prevent false negative classification of patient samples with notable bacteriuria and high specificity to prevent unnecessary culture request. In our study, we researched the detection adequacy of the Sysmex UF-5000 FC analyzer as a screening test for bacteriuria (or UTI). This test was compared with the gold standard of urine culture to assess the potential to use the FC system as a screening test before implementing the labor-intensive and costly test of urine culture.

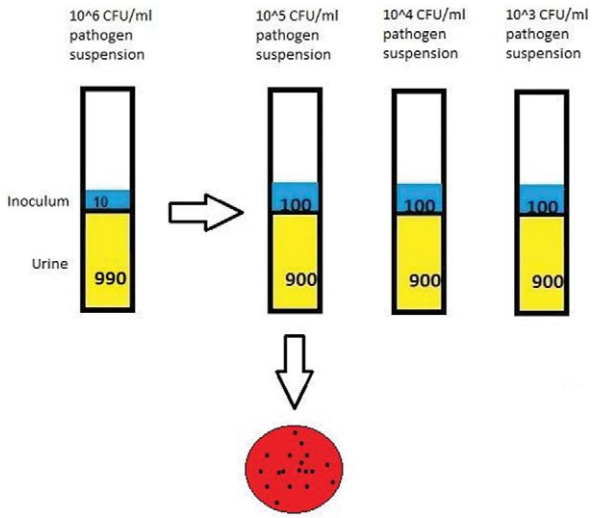
METHODS

This study used standard bacterial and fungal strains with samples from a healthy volunteer without UTI. Urine obtained from a healthy volunteer was used for the research within 1 hour. Simulations of infected urine were created by mixing certain amounts of the following standard bacterial strains with the urine to be tested. In this study, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 25923, *S. aureus* ATCC 43300, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* ATCC 10231 standard strains, one *Lactobacillus* spp., and one *Staphylococcus epidermidis* clinical isolate were used. After the dilution process, 42 urine samples (seven strains × six dilutions) were tested and assessed with two separate methods. Ethical committee approval was received from the Clinical Research Ethics Committee of Gaziantep University (December 18, 2018; 2018/381).

Main Points

- The use of flow cytometry in hospitals can bring lots of advantages, but it is a method that requires times, is laborious, and is expensive.
- We created a simulation model of UTI by creating artificial bacteriuria in our study and found an agreement between the flow cytometric method and urine culture only for the tubes containing 10^5 CFU mL^{-1} pathogen.
- In our simulation model, the flow cytometric system failed to predict bacteriuria; however, further researches such as the fluorescence in situ hybridization technique are needed in this space.

Figure 1. Preparation of pathogen-containing urine dilutions for the urine infection simulation.



Inoculation and Dilution

First, 1 mL of urine was placed in a sterile glass tube and 10 µL was discarded. At this point, a 0.5 McFarland = 10^8 CFU mL^{-1} bacteria (*E. coli*) suspension was prepared in sterile physiological serum (0.9% NaCl). Then, 10 µL of the bacterial solution was mixed with 990 µL urine to lower bacterial density to 10^6 CFU mL^{-1} (1/100). The urine-bacterial solution obtained after this stage was included in 10-time serial dilution studies and after dilutions, urine samples with 10^6, 10^5, 10^4, 10^3, 10^2, and 10^1 CFU mL^{-1} bacterial density were obtained (Figure 1).

Urine Culture

The first solution obtained from the pathogen-urine suspensions in the microbiology laboratory was discarded, and a 10 µL urine with calibrated essence from the second, third, fourth, fifth, and sixth was appropriately inoculated in 5% sheep blood agar and eosin methylene blue agar culture plates. The colonies growing on the culture plates were manually counted after 24 hours of incubation at 35°C and investigated in terms of contamination. Additionally, gram staining was performed on the growing colonies.

Flowcytometric Cell Count

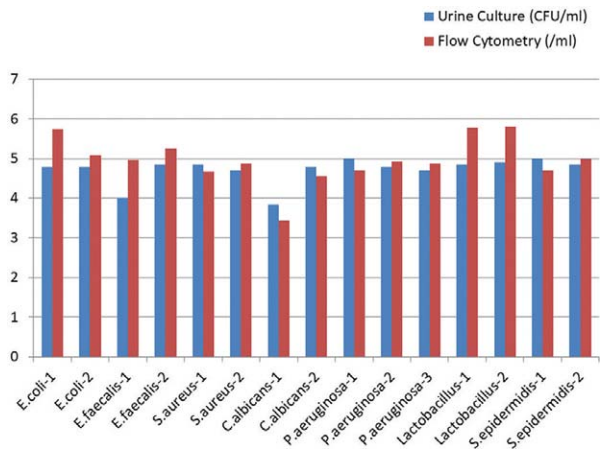
A Sysmex UF-5000i (Sysmex Corporation, Japan) system was used to count pathogen microorganisms in urine. The capacity of the Sysmex UF-5000 system is 105 uncentrifuged urine samples. A total of 2 mL minimum volume is studied, with 0.6 mL urine used in BF mode and 0.45 mL fluid required for aspiration volume in automatic state mode. In our study, 500 µL from each urine tube was investigated in the FC system at the same time. After culture and FC tests were performed with the standard *E. coli* strain first, other standard bacterial and fungal strains were examined.

Table 1. Intraclass Correlation Coefcient (ICC) and Spearman Correlation Coefcient (r) Results

	Spearman r	ICC (95% CI)	*P*
105	r = 0.220; *P* = .430	0.46 (0.05-0.78)	.036*
104	r = 0.251; *P* = .367	0.42 (-0.10 to 0.76)	.054
103	r = 0.077; *P* = .784	0.06 (-0.45 to 0.54)	.413
102	r = -0.257; *P* = .355	-0.22 (-0.65 to 0.31)	.792
101	r = -0.422; *P* = .117	-0.17 (-0.62 to 0.36)	.739

ICC, intraclass correlation coefficient; CI, confidence interval.
*$P < .05$ was considered statistically significant

Figure 2. The number of microorganisms detected by two methods in the simulation of urine containing 10^5 CFU mL^{-1} pathogen (log 10).



Statistical Method

Correlation between the two methods (culture and FC) for bacterial counts was assessed with the in-class correlation coefficient (ICC) and Spearman correlation coefficient (r). All statistical analyses used Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). *P* values <.05 were accepted as statistically significant.

RESULTS

In our study, a significant agreement was observed between the two methods only for the urine dilution containing 10^5 CFU mL^{-1} pathogen (Table 1 and Figure 2).

However, the ICC value was found to be as low as 0.46 (moderate agreement). Regarding other dilutions, no significant correlation was observed between the results of both two methods (Table 1).

DISCUSSION

Though urine culture is the gold standard for the detection of UTIs, the labor-intensive nature and need to wait for at least 24 hours to obtain results have motivated researchers to search for more rapid diagnostic tests.[11,12] For UTIs, a screening test to differentiate negative samples, especially to prevent negative samples not containing pathogens from being included in unnecessary culture processes, will be beneficial from an economic aspect. In Turkey, a 2018 study by Üzmez et al.[13] compared the FC method with the culture method, and they reported 31% of samples coming from all clinics did not need urine culture processes according to their results. They stated that 29.3% of samples from the urology clinic did not require urine culture processes. In this study, they identified that 54 out of 73 patients without proliferation in culture (74%) were positive in the FC system.

De Rosa et al.[8] compared the diagnostic performance of the UF-5000 system with urine culture in 2018. They found that the negative predictive value (NPV) and positive predictive value (PPV) of the UF-5000 system were 87.6 and 66.6 at a cutoff of 40 WBC count μL^{-1} for all samples, respectively. They concluded that the UF-5000 represented a rapid and reliable method for ruling-out UTI and stated that it offers the chance to detect gram negative bacteria in very high agreement with urine culture. However, in their study, they analyzed the results in combination with flowcytometric WBC count results (not alone). That is because they reported UF-5000 system as a reliable method. In another study to rapidly discriminate culture-negative urine specimens from patients with suspected UTI with the UF-5000, researchers obtained a sensitivity of 97.8%, a specificity of 74.6%, a PPV of 46.9%, an NPV of 99.3%, and an agreement of 78.9% with the culture method and stated that it reduced unnecessary urine culture by 61%.[14] However, both cutoff values for bacteria and WBC (bacteria less than 30 μL^{-1} and/or WBC less than 200 μL^{-1}) were included in this study to increase the power of the screening test. In another study, researchers investigated "a new technology to support microbiologists" for interpretation of suspected UTIs using the UF-5000.[15] They used the parameters of squamous epithelial cells, WBC, and conductivity of urine for prediction of UTIs and reported a sensitivity equal to 100% and a specificity equal to 94%, with a total of 69 false positives. They recommended further studies to use this method for rapid detection of UTIs. There are promising studies for rapid detection of UTIs; however, the successful ones are focused on evaluating multiple urine parameters all together. In a recent study, Kim et al.[16] compared the UF-5000 system with urine culture for diagnosis of UTIs. They reported that using a cutoff value of <15 bacteria μL^{-1} to determine whether or not to culture samples, 50.9% of samples were below the cutoff, 94.8 and 99.5% of which presented $<10^4$ and $<10^5$ CFU mL^{-1} of bacterial growth, respectively. They presented this case as a positive result in their study. However, since we can diagnose UTIs at the growth level of 10^3 and 10^4 CFU mL^{-1} in clinical microbiology laboratories, we disagree with the idea that UF-5000 system can be used to eliminate negative samples.

In our study, we investigated only one parameter that is the bacterial count in urine indicating bacteriuria. Although only bacteriuria is not enough to diagnose UTI, it gives a clue of UTI

in combination with physical examination and hematological parameters. So, we created a simulation model of UTI by creating artificial bacteriuria in our study. We found an agreement between the two methods for the tubes containing 10^5 CFU mL^{-1} pathogen. But when the pathogens in the urine decreased, we could not find agreement between the two methods. Significant agreement was observed between the two methods only for the urine dilution containing 10^5 CFU mL^{-1} pathogen (Table 1 and Figure 2) in our study. However, the ICC value was found to be only 0.46 (moderate agreement). No significant correlation was observed between the results of both methods. When we analyze our results, the UF-5000 system gave high positives to almost every urine sample. That is why false negativity is low in the analysis, but false positivity is too high. For example, the UF-5000 system gave a result of 4.96 ± 0.59 ($\log^{10}$) with a bacterial density of 10^5 (5 $\log^{10}$) CFU mL^{-1}. So, we cannot evaluate FC as an appropriate test for diagnosis of UTIs. As a limitation of our study, we did not use clinically obtained UTI samples from our hospital. We prepared the infected urine samples artificially since we wanted to adjust the number of bacteria to definite concentrations for different urine simulation models.

CONCLUSION

The flow cytometric UF-5000 system failed to predict bacteriuria and the risk of UTI in our infection simulation model. However, using the UF-5000 system in combination with other parameters such as WBC and conductivity, we may obtain more promising results in the future. Further research is needed to see the real power of FC methods for the diagnosis of UTIs.

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Original Article

Which is Best for Predicting Uveitis in Behçet's Syndrome: Systemic Immune Inflammatory Index, Mean Platelet Volume, Platelet/Lymphocyte Ratio, or Neutrophil/Lymphocyte Ratio?

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ABSTRACT

Objective: Behçet's Syndrome (BS) is a multisystemic disease characterized by oral and genital ulcers, which can cause vasculitis that can affect all size of the vessels. We aimed to investigate the power of predicting uveitis of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV) and a new parameter, the systemic inflammatory immune index (SII).

Methods: Two hundred four patients with BS were enrolled at Kayseri City Education and Research Hospital, whose follow-up continued from July 2018-September 2020. Thirty-three patients were excluded because of history of cancer, colchicine use, arthritis at the time of diagnosis and complete blood count parameters being excessively higher or lower than the limit values. Of the remaining 171 patients, 35 uveitis patients' NLR, PLR, MPV and SII at the time of uveitis were compared with the results of patients without uveitis.

Results: The sensitivity of NLR in predicting uveitis was calculated as 74.3% and specificity was 64.7%. The sensitivity and specificity of SII, in predicting uveitis, were 62.9% and 65.4%, respectively. The area under the ROC curve for NLR was 0.684 and (P = 0.001). In addition, the area under the curve for SII was 0.662 (P = 0.003). Again for PLR and MPV, the area under the ROC curve was found as 0.566 and 0.428, respectively (P = 0.188 and 0.230, respectively).

Conclusion: There is no specific test that can precisely predict BS and its complications. . These findings suggest that NLR is a better marker than SII, MPV and PLR in predicting anterior uveitis in patients with BS.

Keywords: Behçet's syndrome, uveitis, systemic immune inflammatory index, mean platelet volume, platelet /lymphocyte ratio, neutrophil/lymphocyte ratio

INTRODUCTION

Behçet's syndrome (BS) is a multisystemic disease characterized by oral and genital ulcers, vasculitis, which can be affect any size of vessels, arthritis, especially in the lower extremity, eye involvement, and both vascular and parenchymal damages in the central nervous system.[1] Although it causes quite a variety of morbidity, the etiopathogenesis of the disease has not been clearly elucidated yet.[2] Although the most distinctive form of involvement in the eye is nongranulomatous posterior uveitis; anterior, intermediate uveitis, and optic neuropathy can also occur. There are characteristic vascular involvements such as thrombosis in lower extremity veins and pulmonary arterial aneurysm.[3] Although the pathergy test can be used as an auxiliary test in BS, there is no test that can be used as a gold standard in diagnosis. In addition, there are still no markers that can predict joint, intestinal, central nervous system, eye, and vascular involvements.

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and mean platelet volume (MPV) have been studied in many diseases, especially in cancers and atherosclerotic conditions, in which inflammation is blamed in the etiology.[4–6] In addition, the systemic immune inflammatory (SII) index, which has been a popular marker for the last few years, has also been studied as a marker in predicting diagnosis and prognosis in many diseases, especially cancers.[7–9]

In this study, we aimed to investigate whether SII, NLR, PLO, and MPV predict eye involvement in BS, especially in the form of uveitis, and to examine the sensitivity and specificity of

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these parameters and investigate their superiority to each other.

METHODS

Patient Selection

Two hundred and four BS patients, whose follow-up and treatment were continued in the rheumatology and ophthalmology outpatient clinics between July 1, 2018 and September 1, 2020 at Kayseri City Education and Research Hospital, were included in the study. The diagnosis of uveitis/iridocyclitis of the patients was made by the ophthalmologists in the uvea clinic, which is the ophthalmology subunit of the same hospital (uveitis group). Patients known to have BS and who did not have any uveitis/iridocyclitis during routine rheumatology and ophthalmology examinations were included as the control group.

SII was calculated as neutrophil × platelet/lymphocyte in complete blood count. In people who had uveitis, the complete blood counts at the time of the relevant attack were taken as basis, while the blood counts in the control group were based on the blood counts of the patients in their first outpatient clinic visits. Patients who exceeded some of the following limits in the complete blood count of the patients were excluded from the study: platelet count 150,000-400,000 mm^{-3}, leukocyte count 4,000-10,000 mm^{-3}, neutrophil count 2,000-7,000 mm^{-3}, lymphocyte 1,300-3,500 mm^{-3}, and hemoglobin 11-16 g dL^{-1}. Patients with neurobehçet and pulmonary aneurysmatic changes, articular, intestinal, vascular, or ocular involvements were excluded in the first outpatient clinic examination. Among the patients with other autoimmune diseases (familial Mediterranean fever, ankylosing spondylitis, rheumatoid arthritis, Hashimoto's thyroiditis, etc.), who used colchicine, steroids, and other immunosuppressive treatments within 3 months before their outpatient clinic visit, and those with solid or hematological malignancies were also excluded. One of the 204 BS patients had a history of breast cancer, eight of them had started using colchicine, which was previously started by the family doctor or internal medicine specialist, and seven of them had articular involvement at the time of diagnosis. Also, 16 patients with values higher or lower than the above limit values in complete blood counts were also excluded. Since a total of 33 patients were excluded, analyzes were made on 171 patients.

Demographic data of the patients, C-reactive protein (CRP) and erythrocyte sedimentation rates, MPV, NLR, PLR, and SII were compared, and the sensitivity and specificity data of the relevant data were analyzed.

Main Points

- NLR is found to be a good predictor of uveitis in patients with BS.
- Another effective predictor of uveitis in BS is SII.
- NLR predicts uveitis with a sensitivity of 74.3% and a specificity of 64.7%.
- Although the NLR and SII seem to be a good predictor of uveitis, it should be kept in mind that the diagnosis of uveitis is mainly by an appropriate eye examination performed by experienced specialists.

Consent was obtained from the patients in accordance with the Declaration of Helsinki for participation. This study was approved by the Turkish Republic Ministry of Health, Kayseri City Education and Research Hospital Ethics Committee on November 5, 2020 (study number 43)

Statistical Analysis

Percentages and total percentages are used for the frequencies. Demographic tables were created for these rates. Kolmogorov–Smirnov test was used to check the normal distribution of the data. To compare the groups of continuous data without normally distributed, the Mann–Whitney U test was used. Student t test was used for normally distributed continuous data. Regression models were created to determine whether NLR, PLR, MPV, and SII; age; CRP; sedimentation; and gender were associated with uveitis/iridocyclitis. Correlation tables were made for variables. Receiver-operating characteristics (ROC) curves were drawn, and the area under the curves (AUC) were calculated. In the prediction of uveitis/iridocyclitis, NLR, PLR, MPV, and SII sensitivity and specificity values were chosen to correspond to the best relevant Youden index value calculated as follows: Youden index = sensitivity + specificity – 1. All *P* values were given bivalent. It was performed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM SPSS Corp.; Armonk, NY, USA). Probability values $<.05$ were considered as significant.

RESULTS

Seventy eight of 171 (45.6%) patients who participated in our study were male, and the mean age of the patients was 39.3 ± 10.9 years. Thirty-five of 171 (20.5%) patients had involvement in the form of uveitis/iridocyclitis. In the uveitis group, the number of men was 26/35 (74.3%), while the number of women was 9/35 (25.7%) ($P < .001$). The mean age of the uveitis group was 39.2 ± 12.0, while the mean age of the control group was 39.4 ± 10.7 ($P = .947$). The demographic and clinical data of the patients are summarized in Table 1.

NLR median value of patients in the uveitis group was 2.46 (2.04-2.93), while it was 1.85 (1.45-2.55) in the control group ($P = .001$). The SII median value of the patients in the uveitis group was 640,656.72 mm^{-3} (483,750.00-865,000.00), while it was 487,529.83 mm^{-3} (380,343.75-665,720.69) in the control group ($P = .003$). The PLR median value of the uveitis group was 123.92 (102.69-158.24), while the PLR median value of the control group was 116.46 (92.65-147.70) ($P = .230$). Mean MPV values were 9.00 ± 1.40 and 9.44 ± 1.37 in the uveitis and control groups, respectively ($P = .098$). The sensitivity and specificity for predicting uveitis for the 2.120 cut off value of the NLR were calculated as 74.3% and 64.7%, respectively (likelihood ratio = 2.105). The sensitivity and specificity for predicting uveitis for the cut off value of 563,569.70 of SII, which is another statistical difference between the two groups, were determined to be 62.9% and 65.4%, respectively (likelihood ratio = 1.819). Relevant NLR, SII, PLR, and MPV values in both groups, the power of these values in predicting uveitis, sensitivity/specificity

Table 1. The Demographic and Clinical Data of the Uveitis Group and Control Group

	Uveitis Group (n = 35)	Control Group (n = 136)	*P* value
Age (years), mean ± SD	39.2 ± 12.0	39.4 ± 10.7	.947
Men, no. (%)	26 (74.3)	9 (25.7)	<.001
BMI (kg m^{-2}), median ± SEM	26.52 ± 4.26	26.84 ± 4.13	.965
Smoking, no (%)	20 (57.14)	72 (52.94)	.657
CRP (mg dL^{-1}), median ± SEM	11.89 ± 34.21	5.82 ± 12.56	.094
ESR (mm), median ± SEM	12.26 ± 14.82	13.62 ± 13.00	.593

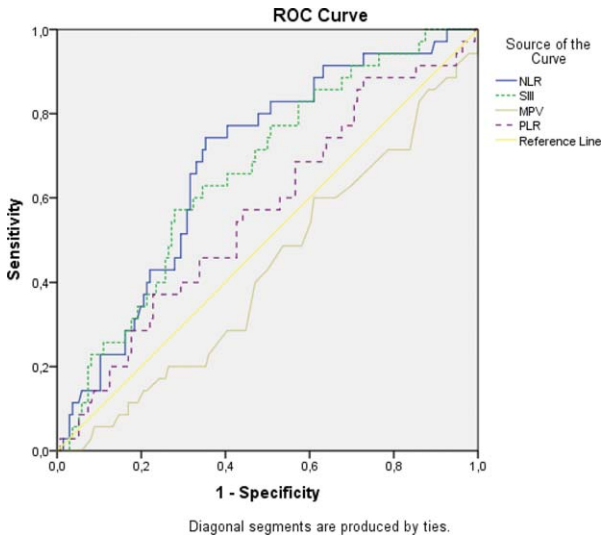
Abbreviations: SD, standard deviation; No, number; BMI, body mass index; SEM, standard error of the mean; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2. The Sensitivity, Specicity, Likelihood Ratios, Positive Predictive Values, and Negative Predictive Values of NLR, SII, MPV, and PLR for Predicting Uveitis

	Uveitis Group (n = 35)	Control Group (n = 136)	*P* Value	Cut Off Value	Sensitivity (%)	Specificity (%)	Likelihood Ratio	PPV (%)	NPV (%)
NLR, median ± SEM	2.46 ± 0.14	1.85 ± 0.07	0.001	2.120	74.3	64.7	2.105	35.1	90.7
SII (mm^{-3}), median ± SEM	640,656.72 ± 39,028.69	487,529.83 ± 23,218.25	0.003	563569.70	62.9	65.4	1.819	31.9	87.3
PLR, median ± SEM	123.92 ± 7.64	116.46 ± 3.65	0.230	121.140	57.1	55.9	1.295	25.0	83.5
MPV (fL), mean ± SD	9.00 ± 1.40	9.44 ± 1.37	0.098	8.850	60.0	39.0	0.983	20.2	79.1

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; SEM, standard error of the mean; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; MPV, mean platelet volume; fL, Fl femtolitre; SD, standard deviation.

Figure 1.. Diagonal segments are produced by ties.



criteria, likelihood ratios, positive predictive values, and negative predictive values are summarized in Table 2.

Area under the ROC curve was 0.684 for NLR (95% confidence interval (CI), 0.591 to 0.776; $P = .001$). In addition, the AUC for SII was 0.662 (95% CI, 0.567 to 0.757; $P = .003$). Also, the area under the ROC curve for PLR and MPV was calculated and found to be 0.566 and 0.428, respectively (95% CI, 0.460 to 0.672 and 0.324 to 0.532; *P* values .188 and .230, respectively) (Figure 1).

When the correlation of uveitis and related variables was examined, it was found to be significant as gender (R: 0.292, $P <$ .001), NLR (R: 0.257, P : .001), and SII (R: 0.227, P : .003). The relationship between the uveitis and gender was the strongest, while the second strongest relationship was in the NLR (Table 3).

DISCUSSION

The most important finding of our study is that NLR is the best predictor of eye involvement in the form of uveitis from MPV,

Table 3. Correlation of Uveitis and Related Variables

	Gender	Age	BMI	CRP	ESR	NLR	SII	PLR	MPV
r value	0.292	-0.014	0.014	-0.010	-0.076	0.257	0.227	0.092	-0.101
P value	<.001	.853	.857	.894	.320	.001	.003	.231	.188

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; MPV, mean platelet volume.

NLR, PLR, and SII in BS, and NLR predicts uveitis with a sensitivity of 74.3% and a specificity of 64.7%. Our other important finding is that SII predicts uveitis with a 62.9% sensitivity and 65.4% specificity, although not as much as NLR. However, it has been observed that MPV and PLR have very limited predictive power of predicting uveitis. Although the aim of this study is to compare the power of predicting uveitis of NLR, SII, PLR, and MPV, it was also seen that one of the most important risk factor for uveitis is male gender, in line with the literature.[10] In a study in which Tugal-Tutkun et al.[11] analyzed 880 patients, it was observed that men were exposed to uveitis more frequently, had earlier ages of onset, and had a more severe and bilateral involvement rate. We see that hematological parameters such as NLR, MPV, SII, and PLR are frequently studied, especially in cancerous diseases. NLR is the most studied parameter among the parameters counted.[12–14] According to a study by Soylu et al.,[15] NLR was found to be associated with clinical and angiographic risk scores in non-ST segment elevated acute coronary syndromes (NSTE-ACS). In the related study, it has been shown that low NLR can be a good predictor for low in-hospital mortality and simple coronary anatomy in NSTE-ACS patients.

MPV is advocated by Atas et al.[16] as a simple measure for indirectly showing platelet activity and thrombotic potential. In this study, it has been shown that MPV and also erythema nodosum are independent risk factors for vascular thrombosis in BS. However, there are studies showing the opposite of this argument. In a study by Balkarlı et al.,[17] active BS patients were compared with inactive BS and healthy controls, and it was observed that MPV was similar in all three groups. Another finding of the study is that NLR was found higher in the active patient group compared to inactive patients and healthy controls. In our study, in parallel with the study of Balkarlı et al., we determined that although MPV is not sufficient in predicting uveitis, NLR is the most sensitive and specific parameter among the parameters examined. Although there are some studies involving NLR, SII, MPV, and PLR for BS and related complications, their comparison with each other has not been clearly examined, and a study analyzing a relatively new data such as SII in uveitis patients in BS could not be found in the literature.

The etiopathogenesis of BS is still unclear, but previous studies have shown that vasovazorum inflammation and endothelial cell activation dominated by neutrophils are the cause of vascular damage.[18] Indeed, neutrophils have been shown to be hyperactive in BS patients, possibly with an additive effect related to HLAB51, and are the main cells that infiltrate not only oral and genital ulcers or erythema nodosum but also other areas such as the eye, central nervous system, and vascular wall.[19] After the neutrophils are activated in BS, there is a serious production of reactive oxygen molecules during nicotinamide adenine dinucleotide phosphate-H (NADPH)-mediated oxidative explosion, and the fibrinogen structure is changed due to inflammation. Finally, it has been revealed that fibrinogen, whose structure has changed, often causes thrombus formation that is tightly adhered to the vessel wall and is resistant to plasmin. It is known that neutrophils are accused of being the blood element that pulls the trigger by a mechanism called neutrophil extracellular trapping at the beginning of all these events.[20] In the light of these data, it is not surprising that NLR, which is the ratio of activated and relatively increased neutrophils to lymphocytes, has higher sensitivity and specificity in predicting uveitis in our study. In addition, the positive predictive value and negative predictive value of NLR were found higher than other parameters examined. The low positive predictive values in the NLR and other parameters in our study are striking. We think that the reason for this is the low number of uveitis cases in BS. Because, as it is known, the positive predictive value is a data obtained by dividing *uveitis + BS* patients, in which the tested parameter is positive, from *all BS* patients, in whom the tested parameter is positive, it is known that PPV is obtained by dividing the true positives by the number of true positives and false positives in the classical formulation (a/a + c). In other words, when the number of uveitis + BS patients is low, the positive predictive value is expected to be low. Conversely, the low number of uveitis + BS patients caused the negative predictive value data to be relatively high.[21] In summary, the low number of cases with uveitis among BS patients was the most important limitation of us. Another limitation of us was only study the involvement in the form of uveitis and not to include other involvements such as retinal vein occlusion and macular edema.

SII, a new inflammatory index, has been tried to be used as a prognostic marker especially for malignancies and inflammatory conditions. According to the results of an analysis by Lolli et al.,[22] it has been shown that SII can be used as an early and easily accessible prognostic marker in metastatic castration-resistant prostate cancer. In addition, it has been shown that SII can be used as a marker in idiopathic sudden hearing loss, which includes inflammatory components and is pulse steroid therapy frequently used for the treatment, and can provide meaningful information in prognosis.[23] In a idiopathic sudden hearing loss study by Ulu et al., SII was also compared with NLR and PLR, and

in the ROC curve analysis, it was observed that the highest value as in the AUC was in NLR. In parallel with this, in our study, we found NLR as the best predictor for uveitis in BS patients.

CONCLUSION

There is no specific test to fully describe and predict BS and its associated complications. NLR was found to be a better marker than SII, MPV, and PLR in predicting uveitis in patients with BS. Although these data have been shown to predict uveitis with an average sensitivity and specificity, it should be kept in mind that the diagnosis of uveitis is mainly an appropriate eye examination performed by experienced specialists.

Ethics Committee Approval: Ethical committee approval was received from the Turkish Republic Ministry of Health Kayseri City Education and Research Hospital Ethics Committee (study number 43, November 5, 2020).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Original Article

Determination of Residual Stress with Diffusion MR Method in Cortical and Trabecular Sections of Human Vertebral Bone Tissue

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ABSTRACT

Objective: The aim of this study was to develop a new method for the determination of residual stress by measuring diffusion coefficient in human vertebral bone tissue using the diffusion MRI method.

Methods: For this study, 75 healthy individuals were recruited and divided into three groups. There were 25 individuals in each group. The age group consists the following: group 1, 15-20; group 2, 40-50; and group 3, 60-70. The vertebrae images of subjects were taken by diffusion MRI. Diffusion coefficient of cortical and trabecular regions was measured on these images, and the results were compared using the Kruskal–Wallis statistical method. Bone densitometry of all subjects was measured, and groups were compared using ANOVA.

Results: The cortical and trabecular diffusion coefficients were compared in groups 1-3. Both diffusion parameters were significantly decreased in groups 1-3. This indicates a decrease in diffusion with increasing age. In the measurements performed with X-ray densitometry, dual energy X-ray absorptiometry (DXA) and Crush values were found to be increased significantly. No significant change was observed in bone mineral content (BMC), bone mineral density (BMD), T, and Z values. Cortical and trabecular diffusion coefficients were decreased with age. BMD and BMC values did not change, but DXA and Crush values were observed to increase with age. Although BMD and BMC values did not change, diffusion reduction may be associated with increasing age.

Conclusion: The results of this study indicate that residual stress that causes nanocrush and later fragility in bone tissue can be determined by measuring diffusion coefficient through the diffusion MR method.

Keywords: Residual stress, vertebral bone, diffusion coefficient, diffusion MR

INTRODUCTION

Stress occurring in materials without any application of external force is defined as residual stress. Residual stress occurs in the natural processes of the material. It occurs during the natural life cycle in the bone tissue and increases the fragility of the bone. The presence of residual stress in bone tissue was reported by Tadano and Okashi.[1] Yamada and Tadano[2] have measured residual stress in bone tissue using the X-ray diffraction method.

In all of the residual stress measurement techniques, the measured samples are taken into the measurement medium in small pieces, and the measurement is made. These methods cannot make the measurement on live tissue. The cortical bone has a complex structure shaped by collagen matrix and mineral particles such as hydroxyapatite. Hydroxyapatite (HAp) in the bone tissue has a hexagonal crystal structure, and X-ray scattering can be used to measure the interplanar spacing of HAp crystals.[3–8]

When the bone tissue is deformed, the variation of the lattice planes of the HAp crystals always changes proportionally. The distance between the lattice planes of the HAp crystals was shown to vary proportionally to the deformation of the bone tissue.[6] HAp crystal tension can be calculated by the deformation of interplanar spacing.[3,7]

Live tissues respond to mechanical stress through potential changes in volume and growth.[9] Measurements by X-ray diffraction in rabbit tibiofibular showed residual stress of 0.1 MPa even in the natural posture.[10] Tanaka and Adachi[11] reported a 2 MPa residual stress in the natural position in cattle coccygeal vertebrae.

According to the results of the study, it is possible to measure residual stress levels that increase the fragility of human vertebral bone tissue in vivo by the diffusion MR method. Known methods for measuring residual stress only measure in vitro. This study will be a new method in this subject.

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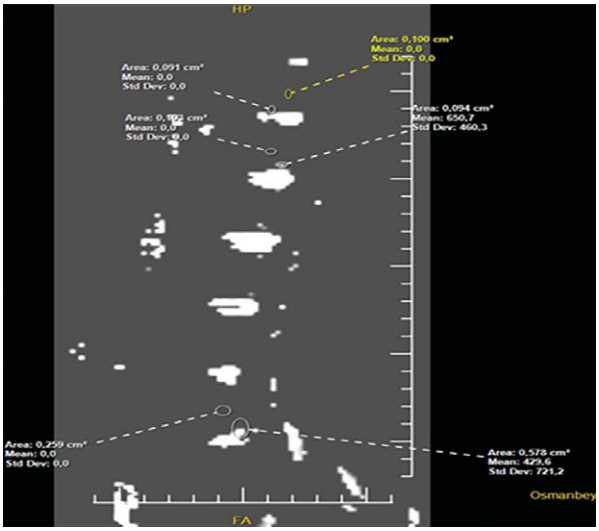
Figure 1. Measurement of diffusion coefficient in vertebra in diffusional MR.



According to the current literature, residual stress in the vertebral bone tissue is measured by in vitro methods, mainly by the X-ray diffraction method. It is not possible to measure living tissue in vivo. This study aims to determine the residual stress measurement in living tissue with the diffusion coefficient.

METHODS

For this study, a total of 75 healthy subjects (individuals) without any bone problems were selected and divided into three groups with 25 individuals in each group. Subjects were divided based on the age group: group 1, 15-20; group 2, 40-50; and group 3, 60-70. The subjects were not administered any drugs, and the vertebrae images were taken by diffusion MRI (Siemens Senfoni 1.5T). Diffusion coefficients of the same regions were measured on these images, and the results were compared with the appropriate statistical method (Kruskal–Wallis). In addition, bone densitometry of all subjects was measured, and groups were compared using ANOVA (Figure 1).

This article does not contain any studies with animals performed by any of the authors.

All procedures in this study involving human participants were performed in accordance with the Ethical Standards of the Institutional Review Board and National Research Committee with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical committee approval was received from the Medical Faculty Ethics Committee of Harran University (April 1, 2016, No. 03-12).

Main Points

- Residual stress is a phenomenon that causes cracks in bone tissue and subsequent fractures.
- Residual stress cannot be measured in living bone tissue using current methods.
- In this study, a method has been developed to measure residual stress in living bone tissue using the diffusion MR method.

RESULTS

Diffusion MR images of cortical and trabecular sections of C2, C7, T1, T12, L1, and L5 vertebrae were taken for the age groups of 15-20 (group 1), 40-50 (group 2), and 60-70 (group 3). Diffusion measurements were made in these sections. The k and m diffusion values were determined in these vertebrae of each group. C2, C7, T1, T12, L1, and L5 vertebrae of k and m diffusion MR values were compared with groups 1-3. In addition, group 1 and group 2, group 1 and group 3, and group 2 and group 3 were compared with each other separately (Tables 1 and 2).

For each sample, dual energy X-ray absorptiometry (DXA), Crush, bone mineral content (BMC), bone mineral density (BMD), T, and Z values were measured (Table 3). These values were also compared between groups. In the 60-70 age group, it was found that the crush value, which is an indicator of fragility, had increased significantly according to the DEXA measurements (8.23), and also the Z score result was found to have decreased significantly in the older age group (–1.06), compared with groups 1 and 2, which were not significant.

DISCUSSION

The presence of residual stress in bone tissue was reported by Tadano and Okashi.[1] Yamato and Tadano[2] measured residual stress in bone tissue by the X-ray diffraction method.

The cortical bone has a complex structure shaped by collagen matrix and mineral particles such as HAp. HAp in the bone tissue has a hexagonal crystal structure, and X-ray scattering can be used to measure interplanar spacing of HAp crystals.[3–8]

When the bone tissue is deformed, the variation of the lattice planes of the HAp crystals always changes proportionally. The distance between the lattice planes of the HAp crystals was shown to vary proportionally to the deformation of the bone tissue.[6] HAp crystal tension can be calculated by deformation of interplanar spacing.[3,7]

Live tissues respond to mechanical stress through potential changes in volume and growth.[9] Measurements by X-ray diffraction in rabbit tibiofibular showed residual stress of 0.1 MPa even in the natural posture.[10] Tanaka and Adachi[11] reported a 2 MPa residual stress in the natural position in cattle coccygeal vertebrae.

According to the current literature, residual stress in vertebral bone tissue is measured by in vitro methods, mainly by the X-ray diffraction method. It is not possible to measure living tissue in vivo. This study aims to determine the residual stress measurement in living tissue with the diffusion coefficient.

In the results of the evaluation, diffusion MR images of three different groups were taken, and diffraction coefficients k and m were determined separately in C2, C7, T1, T12, L1, and

Table 1. Measured k Diffusion Values of the C2, C7, T1, T12, L1, and L5 Vertebrae Cortical Sections in Groups 1-3

	Group 1	Group 2	Group 3	*P*
C2	254 ± 160	257 ± 138	197 ± 123	.152
C7	170 ± 164	182 ± 94	108 ± 92	.028
T1	196 ± 135	175 ± 95	156 ± 59	.028
T12	147 ± 25	100 ± 95	106 ± 83	.023
L1	153 ± 75	127 ± 80	78 ± 57	.004
L5	143 ± 29	100 ± 83	65 ± 20	.000

It is observed that k diffusion values in all vertebrates, except C2, decreased significantly with increasing age.
C2, C7: cortical 2 and 7 vertebral bones; T1, T12: thoracal 1 and 12 vertebral bones; L1, L5: lomber 1 and 5 vertebral bones.

Table 2. Measured m Diffusion Values of the C2, C7, T1, T12, L1, and L5 Vertebrae Medullary (Trabecular) Sections in Groups 1-3

	Group 1	Group 2	Group 3	*P*
C2	450 ± 145	344 ± 146	294 ± 152	.022
C7	420 ± 171	317 ± 152	241 ± 160	.010
T1	234 ± 124	312 ± 134	236 ± 176	.014
T12	254 ± 43	182 ± 159	147 ± 93	.042
L1	240 ± 99	212 ± 62	110 ± 92	.000
L5	193 ± 29	185 ± 59	90 ± 37	.000

It is observed that m diffusion values in all vertebrae decreased significantly with increasing age.
C2, C7: cortical 2 and 7 vertebral bones; T1, T12: thoracal 1 and 12 vertebral bones; L1, L5: lomber 1 and 5 vertebral bones.

Table 3. DXA, Crush, BMC, BMD, T, and Z Values Measured in the Vertebrae of Groups 1-3

	Group 1		Group 2		Group 3		
	Mean	SD	Mean	SD	Mean	SD	*P*
DXA	93	12.8	95	12.7	109	23.97	.010
Crush	2.4	2	3.8	0	7.9	4.2	.025
BMC	56	11	60	13	57	14	.610
BMD	0.97	0.13	1.0	0.13	1.06	0.21	.927
T	-0.7	1.2	-0.6	1.1	-0.5	1.7	.864
Z	-0.69	1.2	-0.78	1.1	-1.06	2.05	.029

It is observed that DXA and Crush values increase significantly with age. There was no significant change in BMC, BMD, and T values, but the Z score result was found to be increased significantly in the older age group, compared with groups 1 and 2.
DXA, dual energy X-ray absorptiometry; BMC, bone mineral content; BMD, bone mineral density; T, maximum bone mass; Z, expresses the mean BMD difference of controls in the same gender and age group as the standard deviation of the patient's BMD results.

L5 vertebrae. In all groups, m diffusion coefficient was found to be greater than k diffusion coefficient on average. It was observed that the diffusion coefficients of C2, C7, T1, and T12 vertebrae were decreased in the 60-70 age group subjects, and both the m and k diffusion coefficients were observed to decrease significantly on average in L1 and L5 vertebra cortical in particular. These results indicate that the loading in the lumbar region is greater, resulting in higher residual stress in this region.

In the 60-70 age group, it was found that the crushing value, which is an indicator of fragility, increased significantly according to the DEXA measurements (8.23), and also the Z score result was found to decrease significantly in the older age group (–1.06), compared with groups 1 and 2, which were not significant. It was about –0.69 and –0.78 in the other groups. Full fragility occurs in values smaller than –2.5. There was no significant difference between the groups in terms of BMC and BMD values.

CONCLUSION

Residual stress is a physical factor that occurs in natural life processes and causes nanocracks in bone tissue. The aim of this study was to develop a new method for measuring residual stress in living bone tissue. In this study, we have developed a new method for the measurement of residual stress in live vertebral bone tissue using the diffusion MR method.

Ethics Committee Approval: Ethical committee approval was received from the Medical Faculty Ethics Committee of Harran University (April 1, 2016, No. 03-12).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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Author Contributions: Concept - C.S.; Design - C.S.; Supervision C.S.; Resources - C.S, M.A.A.; Materials - C.S, A.D.; Data Collection and/or Processing - C.S, A.D.; Analysis and/or Interpretation - C.S.; Literature Search - C.S; Writing Manuscript - C.S. A.D; Critical Review - C.S, M.A.A

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Conflict of Interest: The authors do not have any financial relationship with Harran University Scientific Research Fund, which is the sponsor of the research. The authors have no conflicts of interest to declare.

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Original Article

Remission Rates, Time to Remission, and Related Factors in Adolescents with Major Depressive Disorder

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ABSTRACT

Objective: Major depressive disorder (MDD) is a common disorder in children and adolescents that can cause serious morbidity and mortality. Although response rates to treatment are high, less than half of the adolescents with MDD achieve remission. The present study aims to evaluate remission rates, time to remission, and the predictors of remission in adolescents with MDD.

Methods: This study included 34 adolescents with MDD who were followed-up for a minimum period of 120 days. The adolescents were assessed with the Clinic Global Impression Scale, Beck Depression Inventory, Young Mania Rating Scale, Child Mania Rating Scale, and Screen for Child Anxiety-Related Emotional Disorders at the baseline and at weeks 4, 8, and 12.

Results: 67.6% of the adolescents had at least one comorbid diagnosis. The remission rate at week 12 was 73.5%. The mean time to remission was 72.0 days. The female adolescents achieved a significantly higher remission rate than the males.

Conclusion: The majority of adolescents achieved remission following acute treatment, and that the time to remission for the female adolescents was shorter compared with the males. Remission time does seem neither to be related to the number of medications prescribed nor to the number of comorbid diagnoses.

Keywords: Adolescent depression, treatment outcomes, remission

INTRODUCTION

Major depressive disorder (MDD) with a prevalence of 4-8% is one of the most common mental disorders in children and adolescents.[1,2] Although recovery is usually observed following the first episode of depression that occurs during adolescence, follow-up studies have reported an 80% recurrence rate.[3] The treatment of depression consists of three phases: the acute phase, the continuation phase, and the maintenance phase. The aim of the acute phase is to achieve a rapid improvement in the symptoms, while the continuation phase aims to achieve a sustainable and permanent remission of symptoms. Finally, prevention of a recurrence is the primary objective of the maintenance phase. While the acute and continuation phases are relevant to all patients in the treatment of depression, it is recommended that the maintenance phase only be implemented to selected children exhibiting risk factors to prevent the occurrence of new episodes.[4] If depression is not properly treated, recurrent episodes may continue during an individual's lifetime, leading to an impairment of academic and social life and an increased risk of suicide.[5]

Although the treatment response, which is defined as a 50% improvement from baseline on the standardized rating scales, is taken into consideration in the evaluation of the treatment

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efficacy, the main goal of treatment is to achieve remission, which is an improvement in the symptoms, so that the individual no longer meets the criteria of a depressive disorder and has minimal symptoms.[6] Relapse and recurrence rates increase in patients who respond to treatment but who do not achieve remission. However, the patients who have been successfully treated and who have achieved complete remission will not face such a high risk if their treatment is properly managed.[3] Therefore, achieving remission is crucial for the long-term treatment of depression by reducing the risk of relapse, suicide, and substance abuse, increasing the quality of life and avoiding increased healthcare costs caused by depression.[7]

Short- and long-term changes in symptoms with pharmacotherapy and/or psychotherapy in adolescents diagnosed with MDD have been drawing increased attention recently; however, the data are mostly obtained from naturalistic follow-up studies. Although "response" alone remains insufficient to assess the outcome of treatment, and "remission" has been reported as the gold standard for the efficacy of treatment,[8] the most common criterion to determine the effectiveness applied in clinical studies conducted to date has been "response." In this study, the aim was to determine remission rates, the duration of remission, and predictors of remission obtained as a consequence of acute treatment in adolescents with MDD.

METHODS

This study was designed as a naturalistic and retrospective study. The study protocol was approved by the Ethics Committee of AIBU (Abant Izzet Baysal University) (protocol/serial number: 2018/163). Participants' parents provided a written informed consent before the scales were applied.

Sample

The sample of the study consisted of adolescents between the ages of 12 and 17 who were admitted to the Department of Child and Adolescent Psychiatry at Abant Izzet Baysal University (AIBU) School of Medicine, diagnosed with MDD and treated between 2011 and 2013.

Main Points

- The importance of irritability in adolescent depression may increase the use of atypical antipsychotics in pharmacological treatment.
- Remission rates of adolescents were reported to be between 23 and 63% after 12 weeks of treatment. In this study, the remission rate at week 12 was found to be 73.5%. The ambiguous definition of the concept of remission and different measurement methods that can be used to measure remission may affect the wide range of remission rates.
- There are several factors related to the achievement of remission such as the age of onset, gender, level of functioning, duration of depressive episode, and comorbidities. In the current study, no significant difference was identified in relation to the times in achieving remission according to the number of comorbidities; however, it was found that female adolescents achieved remission in a shorter time and at a higher rate than males.

The inclusion criteria were as follows:

(a) 12-17 years of age;
(b) Meeting the advanced Diagnostic and Statistical Manual of Mental Disorders criteria for MDD;
(c) Existence of follow-up data for at least 120 days;
(d) No missing data in the outpatient clinic records; and
(e) Absence of bipolar disorder, psychotic spectrum disorder, mental retardation, autistic spectrum disorder, substance use disorder, and any neurological disorders.

In addition, it was required that the assessments at the baseline and at weeks 4, 8, and 12 include a Clinic Global Impression Score (CGI), Beck Depression Inventory (BDI), Young Mania Rating Scale (YMRS), Child Mania Rating Scale (CMRS), and a Screen for Child Anxiety Related Emotional Disorders (SCARED). At the last visit, adolescents with a CGI score of 1 or 2 were considered to be in remission.[9]

The number of patients admitted with depressive complaints between the dates is 3,034. Three hundred and twenty-eight of them are considered to meet the diagnosis of MDD according to diagnostic and statistical manual of mental disorders-IV (DSM IV) criteria, and 34 of the MDD patients who met the inclusion criteria mentioned above were included in the study. Among the cases that met the diagnosis of MDD, the most case loss occurred due to the incomplete 120-day follow-up period ($n = 165$) and missing data in the file ($n = 59$).

Assessment Scales

- *BDI*: The BDI is a 21-item multiple choice self-reporting inventory consisting of symptoms and attitudes related to depression. The items have a total summed score range of 0-63, with the higher numbers indicating an increase in the severity of depression. The standard cutoff scores are as follows: 0-9, indicating minimal depression; 10-18, indicating mild depression; 19-29, indicating moderate depression; and 30-63, indicating severe depression. A validity and reliability study in Turkish was performed by Hisli for this scale.[10]
- *SCARED*: The SCARED was developed as a screening tool for both children and their parents that would encompass several categorizations of anxiety disorders: somatic/panic, generalized anxiety, separation anxiety, social phobia, and school phobia. It is accepted that a total score of $\geq$25 may indicate the presence of anxiety disorder.[11] A validity and reliability study in Turkish for this scale was conducted by Çakmakcı.[12]
- *YMRS*: The YMRS is an 11-item tool, which is applied by a clinician. The items on the scale rank symptoms of mania by five clearly defined grades of severity. The YMRS yields a score ranging from 0 to 60, with higher scores representing a more severe psychopathology. It is accepted that a total score of $<$12 indicates euthymia. A Turkish validity and reliability study in Turkish was conducted for this scale by Karadağ et al.[13]
- *CMRS*: CMRS is a 21-item diagnostic screening tool developed by Pavuluri et al.[14] designed to identify the symptoms of mania in children and adolescents aged

Table 1. Comparing Baseline Scales Score of Adolescents

	Male	Female	Total	z	*P*	r
Number of comorbidity	1.7 (1.0)	1.8 (1.3)	1.7 (1.1)	–0.1	.9	–0.017
Baseline CMRS score	7.8 (5.3)	19.8 (13.0)	10.6 (9.0)	–2.5	.01	–0.43
Baseline YMRS	6.5 (5.1)	5.0 (0.0)	6.1 (4.4)	–0.3	.9	–0.293
Baseline BDI	21.9 (7.7)	28.1 (11.1)	24.4 (9.6)	–1.7	.1	–0.189
Baseline SCARED	35.0 (17.0)	41.8 (14.5)	37.7 (16.1)	–1.2	.3	–0.293
Baseline CGI	4.4 (0.7)	4.7 (0.9)	4.5 (0.8)	–1.1	.3	–0.172

Abbreviation: CMRS, Child Mania Rating Scale; YMRS, Young Mania Rating Scale; BDI, Beck Depression Inventory; SCARED, Screen for Child Anxiety and Related Disorders; CGI, Clinic Global Impression Scale.

between 9 and 17. Although a validity and reliability study in Turkish has not been conducted for this scale, it is used for screening mania symptoms by clinicians in Turkey.

- *CGI-Improvement Scale (CGI-I)*. CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened in comparison to the baseline.[15] CGI-1 indicates very much improvement-nearly all better and good level of functioning, and CGI-2 indicates much improvement—notably better with significant reduction of symptoms. In this study, adolescents with a CGI score of 1 or 2 were considered to be in remission.[9]

Data Analysis

The data obtained by the study were evaluated using the Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc.; Chicago, IL, USA). Some of the sociodemographic and clinical categorical variables of the cases were assessed based on numbers and percentage values. A Chi-square test was used to compare the categorical variables. Remission time was recorded on a daily basis and evaluated based on a Kaplan–Meier survival analysis. *P*-values $<.05$ were considered significant.

RESULTS

Thirty-four adolescents were included in the study during the study period. The mean age of the adolescents was 15.3 $\pm$ 0.9. The number of male patients was 20 (58.8%) and female patients was 14 (41.2%). The comparison of the baseline scale scores according to gender is given in Table 1. Nonparametric tests were used in comparisons where the data were not normally distributed (Man–Whitney U Test). When the number of comorbidities, and BDI, CMRS, and CGI scores were compared by gender, significant differences were observed between the CMRS scores ($P = .001$), whereas no significant difference was seen between the other values ($P > .05$).

67.6% of the cases had at least one comorbidity. The most common comorbid diagnosis was anxiety disorder (67.6%). Fifty percent of the cases had a psychopathology in the family history, and it was learnt that 61.8% had presented to other clinics for depressive complaints in the past. 91.2% of the patients were started on medication after the initial evaluation. The most commonly used drugs were atypical antipsychotics (AAP) (79.4%) and selective serotonin reuptake inhibitors (SSRIs, 55.9%). The remission rate was 73.5% (n = 25) at week 12 of the treatment. Female adolescents had significantly higher remission rates than males (Chi-square = 6.8, $P = .01$, $\pi = 0.5$). A posthoc power analysis based on Chi-square results achieved 0.60 power. The mean time to remission in our sample was 72.0 (SD 22.9) days (mean: 55.7 $\pm$ 20.7 days for females and 78.3 $\pm$ 20.9 days for males, Mann-Whitney U test, Z = –2.4, $P = .03$). A posthoc power analysis based on Mann–Whitney U test results achieved 0.99 power. Comparison of remission time in girls and boys according to comorbidities was done with Kaplan–Meier survival analysis (Figures 1 and 2). The Kaplan–Meier test revealed that the remission time did not differ based on the number of comorbidities.

DISCUSSION

In this study, which examined time to remission and factors related to remission in the acute treatment in adolescents with MDD, the most frequently prescribed drug for depressive adolescents was found to be AAP. Although the clinical appearance of depression in children and adolescents is similar to adult depression in terms of core symptoms, it also displays some important differences. Instead of expressing depressive feelings, children and adolescents may exhibit emotional volatility, irritability, low frustration tolerance, anger outbursts, and related destructive behavior.[16,17] While cognitive behavioral therapy is recommended as the first-line treatment for mild to moderate MDD in children and adolescents, SSRI are recommended as the first-line treatment in moderate to severe MDD cases.[18] AAPs are used for adjuvant treatment in resistant depression and are prescribed as an additional treatment to an antidepressant.[1] Although SSRIs are recommended as the first choice in the pharmacological treatment of MDD, it was thought that prescription of AAPs rather than SSRIs in the present study may be due to the fact that irritability is at the forefront in the clinical appearance of adolescent depression or that parents put higher emphasis on irritability, especially in

Figure 1. Time to remission according to number of comorbidities in males.

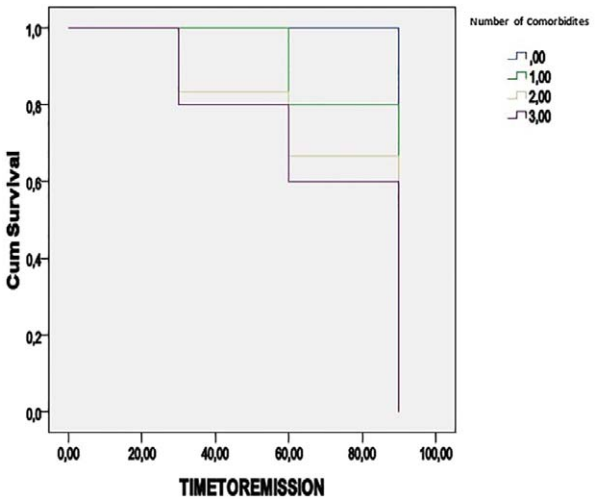
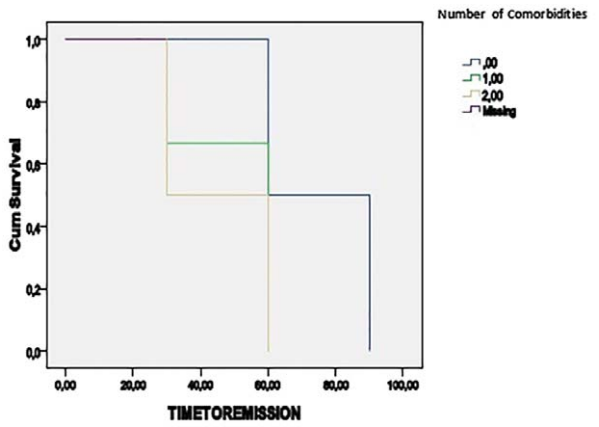


Figure 2. Time to remission according to number of comorbidities in girls.



girls, and there is an expectation that it should resolve as soon as possible. In support of this proposition, female adolescents did not show a significant difference in the YMRS as evaluated by a clinician, while they received significantly high scores from the CMRS completed by their parents.

Remission rates of adolescents were reported to be between 23 and 63% after 12 weeks of treatment.[19] The treatment for adolescents with depression study (TADS) reported that the remission rate to be 23% in adolescents after 12 weeks of acute treatment. However, at week 36, remission rates were increased to 60%, demonstrating the importance of maintenance therapy.[20] In the current study, the remission rate at week 12 was found to be 73.5%. One of the issues most widely discussed in the literature is the ambiguous definition of the concept of remission. Different measurement methods can be used to measure remission, which is defined as a state of minimal to no symptoms with restoration of normal functioning. Remission measurements in clinical trials are commonly based on the cutoff scores from standardized scales. For example, a Hamilton Depression Score of seven or less, a Montgomery-Asberg Depression Scale score of 10 or less, or a Clinical Global Impression (CGI) score of one or two is typically defined as remission. Some studies in the literature relating to child and adolescent psychiatry have used a child depression rating scale score of 28 or lower to define remission.[20–24] The remission rates obtained in the present study may be high as we adopted a more flexible definition of remission (CGI 1 or 2) as suggested by the American College of Psychopharmacology.[25] In addition, we think that the long time allocated to a patient (45 minutes for each interview) in our polyclinic, which is also an education clinic, contributes to the high remission rates by strengthening the therapeutic relationship.

In general, factors related to the reduction in symptoms and the achievement of remission are the age of onset, gender, level of functioning, duration of depressive episode, number of comorbidities, existing melancholic features, suicidal ideation and feelings of hopelessness, and the patient's expectations from the treatment.[26–28] In this study, no significant difference was identified in relation to the times in achieving remission according to the number of comorbidities; however, it was found that female adolescents achieved remission in a shorter time and at a higher rate than males. A recent study that investigated the course of the acute phase symptoms of depressed teens enrolled in TADS indicated that a group consisting of adolescents with severe depression achieved early improvement with treatment (high severity-early improvement group). Most of the patients in the high severity-early improvement group in the said study were female.[5] In line with this finding, it was observed, although at a level of significance, that female depressive adolescents had higher depression scores than the males at the beginning of treatment; however, they achieved remission in a shorter time compared with the males.

The current study had several limitations. The results obtained in this study may not be generalized as it was a single-center study conducted on a selected clinical sample. The small sample size and the fact that the scales used are based on self-reporting are amongst those limitations. The short follow-up period can also be considered as a limitation. The remission achieved at week 12 may be a spontaneous remission, or a short-term remission that will be followed by a relapse during a longitudinal follow-up.

The data obtained in this study consist of naturalistic and retrospective data. It is recognized that a placebo response is higher in such studies. The findings need to be supported by multicentered longitudinal studies with a larger sample size.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Abant İzzet Baysal University (AIBU) (protocol/serial number: 2018/163).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Original Article

Optimal Timing of Ultrasound for the Diagnosis of Developmental Hip Dysplasia in Infants: 1st or 5th Week?

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ABSTRACT

Objective: Ultrasonography (US) is a useful, easy, and accurate screening method for the diagnosis of neonatal developmental dysplasia of the hip. The purpose of this prospective and cross-sectional study is to determine the optimal timing of US for the evaluation of the hip joints in newborns.

Methods: We enrolled consecutive 27 [18 girls (66.7%) and nine boys (33.3%)] newborns in this study. Two experienced radiologists (Ş.T. and M.Ö.) performed standard hip US examinations at the 1st and 5th weeks of age according to the method described by Graf. We assessed the relationship between femur head and acetabulum and compared the results of evaluation obtained between the 1st and 5th weeks. Additionally, we evaluated the agreement between the two radiologists.

Results: None of the babies were found to have subluxation or dislocation by clinical examination. The US measurements regarding the ossification and the diameter of femur head, bony, and cartilaginous roof at the 1st and 5th weeks were similar (for all infants, $P > .05$). In our series, no hip was defined as Graf's type IIb or higher. In total, four (14.8%) right hips and six (22.2%) left hips (total 10 hips) were classified as Graf's type IIa (physiologically immature) at the 1st week of evaluation. A total of seven hips spontaneously returned to their normal positions during the following 4 weeks. However, two (7.4%) right and one (3.7%) left hip joints were still classified as type IIa at the 5th week of evaluation. Graf type of hips was reported as similar in all the infants by the 1st and 5th week of measurements ($n = 54$, $P > .05$, for each). There was no interobserver variability between the two radiologists with respect to Graf's classification ($\kappa > 0.81$). The blunt/round shape of acetabular rim defined in 10 hips at the 1st week was improved to an angular shape in the eight hips at the 5th week ($P = .008$).

Conclusion: Early US screening along with normal physical examination can diagnose some hip disorders in babies. Most of the abnormal findings detected at the 1st week of US screening recovered spontaneously at the 5th week. Infants with normal US measurements at the 1st week may be excluded from the follow-up, and those with suboptimal findings may be monitored by physical examination and repeated US scans.

Keywords: Hip dysplasia, optimal timing, ultrasound

INTRODUCTION

Developmental dysplasia of the hip (DDH) is one of the most common causes of musculoskeletal disabilities in children. The abnormal development of the femoral head and acetabulum covers a wide spectrum of anatomical abnormalities from thin acetabular dysplasia to nonreducing hip dislocation. Because the disease is mainly a developmental defect, the former term "congenital dysplasia of the hip" was discarded.[1] The incidence varies from 1 to 20 cases per 1,000 live births depending on some factors such as the examination methods and timing of assessment.[2] Most studies report that girls are more affected than boys, and the left hip is more frequently dysplastic than the right one.[2–8]

The etiopathogenesis of DDH is multifactorial. Some risk factors such as female gender, a positive family history, primiparity, presence of a large fetus or multiple fetuses, presentation of breech, oligohydramnios, neuromuscular diseases, or other musculoskeletal disorders have been described for DDH. Additionally, it has been reported that joint laxity increases in infants who are exposed to maternal estrogens in the perinatal period.[2,3]

An accurate and timely diagnosis and treatment improve the clinical outcomes for this disorder.[9–12] The instability examination defining functional or morphological hip defects should be performed shortly after birth. The American Academy of Pediatrics recommends that all newborns should be clinically

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assessed for DDH in the first few days of life.[13] The physical examination, including asymmetric folding, abduction restriction, and provocative testing, such as Piston test and Ortolani and Barlow maneuvers, still hold a diagnostic value.[11,14,15] However, these methods can only detect subluxation or dislocation. Moreover, it is reported that neonatologists cannot detect about half of the unstable hips by using these examinations.[16] At this point, ultrasonography (US) can be considered as a useful, easy, and accurate screening method for the diagnosis of neonatal DDH. The relationship between the femur head and acetabulum can be assessed by standard static,[17–19] early dynamic, or modified dynamic US methods.[20–22] US allows the visualization of the cartilage parts that are not visible on plain radiographs and can effectively distinguish mild instability or acetabular immaturity.[23,24]

Two different screening programs can be planned by using sonographic imaging of the hip: selective programs screen newborns with identified risk factors or those with abnormal clinical examinations, and universal programs screen all the newborns.[13] However, the optimal timing of the US scan remains a controversial matter. Underdiagnosis can lead to complicated and debilitating hip deformities in infancy and childhood, whereas overdiagnosis may result in an unnecessary follow-up and increased parental concerns.[25,26]

The purpose of this article is to compare the results of 1st and 5th weeks of US findings of newborns.

METHODS

We conducted this study in accordance with the principles of Helsinki Declaration in the Niğde Hospital of Ömer Halisdemir University, Turkey. Children's legal guardians provided an informed consent for participation, and Erciyes University, Faculty of Medicine, Kayseri Turkey "Clinic Investigations Of Ethics Committee" dated February 9, 2018 with decision no. 2018/73 was approved this study's protocol and design.

We planned a universal screening by US and enrolled 27 [18 (66.7%) girls and nine (33.3%) boys] consecutive infants in this study. There was no preterm birth (defined as a baby born before 37 weeks according to WHO),[27] low body weight (defined as less than 2,500 g according to WHO),[28] and malformation or deformity in infants. The infants were clinically examined by the same pediatrician on the first day of the life to detect DDH by using Piston test, Ortolani and Barlow maneuvers, asymmetric folding, and abduction restriction. None of them were found to have subluxation or dislocation by clinical examination.

Main Points

- In this study, we compared 1st-week and 5th-week US findings in order to find developmental hip dysplasia in infants.
- After the clinical examination, all the infants underwent US.
- Two experienced radiologists assessed the Graf's scanning and measurements of alpha and beta angles, femur head, ossification, acetabulum, rim, labrum, joint capsule, and type of hip both in 1st and 5th weeks.
- In the 1st week, 18.5% of infants showed blind acetabular rim and physiologically immaturity, while 3.9% and 5.6% for 5th week, respectively. Most of the hips recovered spontaneously at the 5th week.
- Additionally, alpha and beta angles were improved.

Two experienced radiologists performed US examinations by using a linear probe (7.5 MHz Toshiba Aplio 300, Japan). Two serial measurements were performed at the 1st and 5th weeks for all the babies. The relationship between femur head and acetabulum was assessed according to the Graf's scanning and measurement method.[17–19] The transducer was placed on the anatomic coronal plane, and the view was obtained in the physiological neutral position (15°–20° flexion) or the 90° flexed position of the hip. The rounded structures of the hip joint were defined by the transducer's forward and backward motions from the base position. The top edge of the transducer was rotated from 10° to 15° in an oblique coronal plane to view the ilium in the straight position. The calcified nucleus of femur head, the chondro-osseous junction, the lower limb of ilium, acetabular edge, bony and cartilaginous acetabular roofs, acetabular rim and labrum, hip joint capsule, and synovial fold were identified as the anatomical landmarks.

In all the infants, a sonogram containing the iliac line, a triradiate cartilage, and an apparent acetabular labrum was printed out as a standard plane.[13–16] These frozen sonograms were used to bilaterally measure the α and β angles as the indicators of bony and cartilage acetabular roofs, respectively. The α angle was defined as the angle between the acetabular roof and the vertical cortex of the ilium in the coronal plane. An α angle less than 60° reflecting a shallow acetabulum was considered as abnormal. The β angle was defined by a line drawn through the vertical ilium and the cartilaginous acetabular labrum. A β angle greater than 55° was accepted as abnormal.[2] The acetabular rim was classified as angular (sharp), round/blunt, and flat, whereas the bony acetabular roof was classified as good, incomplete, and poor.

Statistical Analysis

This study had cross-sectional and interventional components. We performed statistical analysis by using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). We used Chi-square and Fisher's exact tests to compare the categorical variables. Moreover, we used the McNemar test to determine the change in the frequency or percentage of categorical variables between the 1st and 5th weeks of evaluation. We employed Wilcoxon signed-rank test to compare the Graf's α and β angles between the 1st and 5th weeks' measurements. We evaluated the agreement between the two radiologists by using κstatistics. $P < .05$ was considered as significant in each test.

RESULTS

We included 27 [18 girls (6.7%) and nine (33.3%) boys] infants in the study. In two series of measurements, the femoral head diameter, acetabular labrum development, and positions were normal in all the infants (Table 1). There was an incomplete bone roof in the 1st and 5th weeks for the right and left hips of

Table 1. Gender, Femur Head Diameters, and Acetabular Labrums at the 1st and 5th Weeks

Features	Subgroups	Frequency	%			
Gender	Girls	27	66.7			
	Boys	9	33.3			
		1st Week		5th Week		
Femur Head Diameter		Frequency	%	Frequency	%	*P*
Right	Normal	27	100.0	27	100.0	1.000
Left	Normal	27	100.0	27	100.0	1.000
		1st Week		5th Week		
Acetabular Labrum		Frequency	%	Frequency	%	
Right	Normal	27	100.0	27	100.0	1.000
Left	Normal	27	100.0	27	100.0	1.000

Table 2. Bone Roofs at the 1st and 5th Weeks

		1st Week		5h Week		
Bone Roof		Frequency	%	Frequency	%	*P*
Right	Complete	26	96.3	26	96.3	1.000
	Incomplete	1	3.9	1	3.9	
Left	Complete	26	96.3	26	96.3	1.000
	Incomplete	1	3.9	1	3.9	
Total	Complete	52	96.3	52	96.3	1.000
	Incomplete	2	3.9	2	3.9	

one (3.9%) infant (Table 2). With regard to the cartilaginous roof, none of the babies had displaced hips. However, both hips were noted as short and wide in one (3.9%) baby at the 1st week, and in another baby (3.9%), it was noted at the 5th week. The shape of cartilaginous roof was similar between the 1st and 5th week of evaluations of the left and right hip joints (Table 3). The shape of the acetabular rim was blunt/round in the right hips of four (14.8%) infants at the 1st week and in the right hips of one (3.9%) infant at the 5th week. Similarly, the blunt/round structure was shown in the left hips of six (22.2%) infants at the 1st week and one (3.9%) infant at the 5th week. There was no difference between the 1st and 5th weeks' separate measurements of the right and left hips ($P > .05$, for each). A further analysis was performed considering the total number of hips on both the sides (n = 54). The blunt/round shape of acetabular rim defined in the 10 hips at the 1st week was improved to an angular shape in the eight hips at the 5th week ($P = .008$, Table 4).

In our series, no hip was classified as Graf's type IIb or higher. Moreover, four (14.8%) right hips and six (22.2%) left hips (total of 10 hips) were classified as Graf's type IIa (physiologically immature) at the 1st week. In total, seven hips spontaneously returned to the normal position during the following 4 weeks. However, two (7.4%) right and one (3.7%) left hip joints were still classified as type IIa at the 5th week of evaluation. Graf type of hips was reported as similar in all the infants by the measurements at the 1st and 5th weeks (n = 54, $P > .05$, for each) (Table 5). The boys and the girls had the same hip types at the 1st and 5th weeks ($P > .05$, for each). The Graaf's α and β angles were significantly different between the calculations of 1st and 5th weeks ($P < .01$, for each, Table 6). There was no interobserver variability between the two radiologists with respect to Graf's classification ($\kappa > .81$).

DISCUSSION

The results of this study show that the bilateral femur head diameter, acetabular labrum development, and position were in the normal limits, consistent with the normal measurements occurring at the age of infants in the 1st and 5th weeks. There were no suboptimal results for any of the infants with respect

Table 3. Cartilaginous Roofs at the 1st and 5th Weeks

		1st Week		5th Week		
	Cartilaginous Roof	**Frequency**	**%**	**Frequency**	**%**	*P*
Right	Covers the femoral head (long, narrow)	26	96.3	26	96.3	1.000
	Short, wide	1	3.9	1	3.9	
Left	Covers the femoral head (long, narrow)	26	96.3	26	96.3	1.000
	Short, wide	1	3.9	1	3.9	
Total	Covers the femoral head (long, narrow)	52	96.3	52	96.3	1.000
	Short, wide	2	3.9	2	3.9	

Table 4. Acetabular Rims at the 1st and 5th Weeks

		1st Week		5th Week		
	Acetabular Rim	**Frequency**	**%**	**Frequency**	**%**	*P*
Right	Angular	23	88.5	26	96.3	.250
	Blind/round	4	11.5	1	3.9	
Left	Angular	21	77.8	26	96.3	.063
	Blind/round	6	22.2	1	3.9	
Total	Angular	44	81.5	52	96.3	.008
	Blind/round	10	18.5	2	3.9	

Table 5. Type of Hips at the 1st and 5th Weeks

		1st Week		5th Week		
	Type of Hip	**Frequency**	**%**	**Frequency**	**%**	*P*
Right	Type I mature	23	85.2	25	92.6	.687
	Type IIa physiologically immature	4	14.8	2	7.4	
Left	Type I mature	21	77.8	26	96.3	.063
	Type IIa Physiologically immature	6	22.2	1	3.9	
Total	Type I mature	44	81.5	51	94.4	.065
	Type IIa physiologically immature	10	18.5	3	5.6	

to bone and cartilaginous roofs. However, researchers had previously reported immature developments for femur head diameter and acetabular labrum.[22,23,29–31] In our study, the Graf's α and β angles showed statistically significant improvement between the 1st and 5th weeks. However, there was no unilateral improvement in the acetabular rim between the 1st and 5th weeks' measurements. We attributed this result to the small number of the patients. Hence, we repeated the analysis over the number of bilateral total hips. This analysis revealed that the blunt/round acetabular rim shape, which was defined in the 10 hips at the 1st week, became angular in eight hips at the 5th week. Only two hips remained abnormal at the 5th week. Palliative care and follow-up were planned for these infants. The bone roof of one baby was bilaterally incomplete at the 1st and 5th weeks. It was suggested that this baby should be monitored with palliative care and periodic checkups.

Table 6. Graaf's Alpha and Beta Angle Calculations at the 1st and 5th Weeks

Graaf's Angles		1st Week		5th Week		
		Mean ± SD	Median; Range	Mean ± SD	Median; Range	*P*
Alpha	Right (n = 27)	59.9 ± 1.6	60; 57–64	61.3 ± 2.3	60; 58–67	.007
	Left (n = 27)	59.4 ± 2.7	60; 50–64	60.9 ± 3.0	60; 53–68	.008
	Total (n = 54)	59.7 ± 2.2	60; 50–64	61.1 ± 2.6	60; 53–68	.000
Beta	Right (n = 27)	46.1 ± 6.2	46; 35–67	42.7 ± 4.8	42; 34–55	.001
	Left (n = 27)	46.8 ± 5.5	48; 37–63	42.4 ± 4.7	43; 32–53	.000
	Total (n = 54)	46.4 ± 5.8	47; 35–67	42.6 ± 4.7	42; 32–55	.000

We have previously emphasized that US is a sensitive method that is used in the screening programs for the diagnosis of DDH in many countries. However, despite its advantages, it is still not recommended as a universal screening strategy worldwide because of its disadvantages such as high cost–benefit ratio, observer-related nature, and overdiagnosis.[31] The overdiagnosis of DDH is a more common problem when US is used in especially the first 6 weeks of the life.[23] Additionally, the previous data suggest that overdiagnosis in the first 6 weeks may be due to the different interobserver evaluations. Hence, some researchers noted that an early screening of the US would impose unnecessary monitoring and, hence, anxiety in the family. It also would increase the burden of radiology, orthopedic, and neonatal clinics.[23]

It should be noted that it is difficult to screen the children after the neonatal period in some countries. We planned a universal screening study focusing on the efficacy of early US measurements in detecting the hip problems. We implemented US measurements in two different, but early weeks of life. In our study, all the infants were examined by a pediatrician, and none of them had signs of subluxation or dislocation. However, US measurements have provided suboptimal findings for some infants. We conclude that early US screening can diagnose subtle hip disorders. When we compared the US measurements performed between the two different weeks, the statistical analysis showed that two series of US findings were almost similar. Some findings that were detected in the 1st week and accepted as immaturity improved in the 5th week. Therefore, we interpreted that infants with optimal hip findings according to the US measurements of 1st week can be removed from follow-up. Additionally, infants with suboptimal findings can be followed-up by physical examination and repeated US scans. In our study, there were no differences between the two radiologists.

There are some limitations of our study. First, we believe that our small patient population did not allow us to take some results that were previously obtained in the larger patient series. For example, none of the babies in our study had displaced cartilage roof. Additionally, the shape of the cartilage roof was short and wide in only two infants. In the literature, more serious and high-grade DDH cases have been reported in many babies.[22,23,29–31] On the contrary, most of the studies showed that the girls were more affected than the boys, and the left hip was more dysplastic than the right one,[2–8] whereas our study did not reveal any difference. Second, none of our infants had been classified as Graf IIb or higher. Third, the follow-up period of our study was relatively short.

CONCLUSION

We believe that an early UG screening along with normal physical examination can diagnose hip disorders in the babies. When we compare the US measurements of two separate weeks, we observed that most of the abnormal findings detected at the 1st week can be recovered spontaneously at the 5th week. Infants with normal US measurements at the 1st week may be excluded from the follow-up, and infants with suboptimal findings may be monitored by physical examination and repeated US scans. We state that early UG screening is useful.

Ethics Committee Approval: Ethics committee approval was received from the ethics committee of Erciyes University, Faculty of Medicine, Kayseri Turkey "Clinic Investigations Of Ethics Committee" (date of February 9, 2018; decision 2018/73).

Informed Consent: Written informed consent was obtained from children's legal guardians who participated in this study.

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Original Article

Management of Patients with ST-Segment Elevation Myocardial Infarction during the COVID-19 Pandemic

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ABSTRACT

Objective: Elective operations had to be postponed due to the COVID-19 pandemic that emerged in the last quarter of 2019 and affected the whole world in a short time. However, for emergencies such as myocardial infarction (MI), unfortunately, this is not possible. We aimed to evaluate the management of ST-segment elevation myocardial infarction (STEMI) before and during the COVID-19 pandemic.

Methods: One hundred and eleven consecutive patients with STEMI between April 2020 and May 2020 and 149 patients with STEMI 1 year before the pandemic in the same period were included in the study. Groups were compared in terms of the treatments applied, pre–post-dilatation, duration of the procedure, hospitalization, and the primary end-point. Death due to MI or complications of MI was the primary end-point.

Results: The mean age of the patients was 59.7 ± 12.3 (n = 195 [75%] male). The two groups were similar in terms of gender, diabetes mellitus, hypertension, hyperlipidemia, smoking, and laboratory results. Although the median duration of the door balloon in the pandemic was similar (39 and 37 minutes, respectively; $P = .342$), the procedure times were shorter, the mean total hospitalization times were longer, and the differences were statistically significant ($P = .022$ and $<.001$, respectively). In the study group, 68 patients had pre-dilatation and 30 had post-dilatation during the procedure. The two groups were similar in terms of the primary end-point ($P = .196$).

Conclusion: Percutaneous intervention should be the routine procedure to STEMI patients during the pandemic period, despite the positive possibility of COVID-19 and the risk of transmission.

Keywords: ST-segment elevation myocardial infarction, COVID-19 pandemic, percutaneous coronary intervention

INTRODUCTION

Acute coronary syndromes (ACSs) may be a complication of COVID-19 or primarily due to a plaque rupture, ulceration, or dissection.[1–3] Regardless of the reason, in the case of ST-elevation, revascularization of the patient as soon as possible is the primary goal.[4] In principle, if you are in a center where invasive procedures can be performed, you take the patient to the primary percutaneous interventional catheter laboratory; if you do not have such a possibility, you either refer the patient or give thrombolytics and transfer to the invasive center for facilitated percutaneous coronary intervention (PCI).[5,6] These mentioned procedures have been accepted for the period before the COVID-19, and there is no definite consensus on the management of patients with ACS during the COVID-19 pandemic period.[7]

We aimed to compare the patients with ACS in the COVID-19 period and before in terms of treatment in our clinic that is an invasive center.

METHODS

A total of 111 consecutive patients, followed in coronary intensive care unit due to ST-segment elevation myocardial infarction (STEMI) between April 2020 and May 2020, and 149 control patients who were similar in age, gender, and comorbidity and were hospitalized with the same diagnosis before the pandemic in the same period (April 2019 and May 2019) 1 year ago were included in this retrospective study. In our clinic, all patients were diagnosed STEMI with minimum 24 hours of follow-up in the intensive care unit. Venous blood samples of the patients were taken and analyzed using appropriate methods on admission and during hospitalization.

Kidney and liver function tests, lipid profiles, cardiac troponin and creatine kinase-MB (CK-MB) values, complete blood counts, brain-natriuretic peptide (BNP), and C-reactive peptide level of all patients were recorded. All patients underwent coronary angiography during their hospitalization and required percutaneous intervention. The time from hospitalization to

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Table 1. Baseline Characteristics of Groups

Parameters	Control Group (n = 149)	Study Group (n = 111)	*P*
Age, years	59.4 ± 12.8	60.2 ± 11.6	.626
Male, n (%)	110 (74)	85 (76)	.612
Hypertension, n (%)	76 (51)	54 (49)	.976
Diabetes mellitus, n (%)	64 (43)	46 (41)	.899
Smoking, n (%)	46 (31)	23 (21)	.067
Hyperlipidemia, n (%)	58 (39)	42 (38)	.898

angiography, the use of stents or balloons, and whether pre–post-dilatation was performed, and the amount of opaque used and whether opaque nephropathy developed during follow-up and the patient's outcome were noted. Opaque nephropathy was defined as an increase in >25% or >0.5 mg dL^{-1} of serum creatinine from baseline 48 to 72 hours after contrast medium administered for diagnostic or therapeutic purposes. The primary end-point of the study was death due to MI or complications of MI.

Hypertension was defined as patients' systolic and diastolic blood pressures >140/90 mmHg or if the patient was taking any antihypertensive medication. Diabetes mellitus (type 2 DM) was defined as having a previous diagnosis of DM or using antidiabetic medication, or fasting blood glucose ≥126 mg dL^{-1} or HbA1c >6.5%.

The study was approved by the Clinical Research Ethics Committee of the Ministry of Health of our country and local Clinical Research Ethics Committee of the Adana Health Practice and Research Center (No.: 799, date: April 22, 2020). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Statistical Analysis

Kolmogrow–Smirnow test was used to determine whether variables were homogeneously distributed. Continuous variables were expressed as mean ± standard deviation and compared using Student's t test and Mann–Whitney U test for variables without normal distribution. Categorical variables were presented as total number and percentages and compared using the chi-square test and Kruskal–Wallis test. Receiver operating characteristics (ROCs) curve analysis was used to demonstrate the predictive value of variables in primary end-point. A two-tailed *P* value of <.05 was considered as statistically significant, and 95% confidence interval (95% CIs) were presented for all odds ratios. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Corp.; Armonk, NY, USA).

Main Points

- Despite the risk of transmission during the COVID-19 outbreak, primary percutaneous coronary intervention (PCI) was continued for STEMI patients.
- It was determined that the duration of PCI was shorter.
- It was determined that the rate of opaque nephropathy was lower.
- It was determined that in-hospital mortality was similar.
- It was once again determined that the simple and fastest procedure for STEMI patients is the best.

RESULTS

A total of 260 patients (mean age, 59.7 ± 12.3, 195 males [75%]) were included in this retrospective study. Baseline characteristics of patients and diagnosis on admission were summarized in Table 1.

Laboratory parameters, angiographic properties, and hospitalization times of patients are listed in Table 2. There were not any differences in terms of routine biochemical results, whole blood count tests, and cardiac markers between the two groups. STEMIs included in the study were transferred from the emergency department directly to the catheter laboratory. Although we found a trend toward an increase in door balloon time during the pandemic period, this was not significant. The procedure time was shorter for those who applied during the pandemic period. Pre- and post-dilatations were also less preferred in this group. Considering the length of stay in the intensive care and cardiology service, it was seen that the circulation was faster, and the hospitalization period of the patients was shorter in the prepandemic period. The amount of opaque material used during angiography was less in patients in the pandemic period, and as a result, the rate of opaque nephropathy was statistically significantly lower in the study group compared to the control group. The two groups were similar in terms of the primary end-point.

ROC curve analysis determined that intensive care unit hospitalization time was the only independent predictor of primary end-point (area under curve (AUC): 0.989; CI 95%: 0.967-0.998; *P* = .007) (Figure 1).

DISCUSSION

Although the COVID-19 viral infection, caused by coronavirus, usually manifests with respiratory symptoms caused by severe pneumonia, cardiac involvement can be seen in cases and, when seen, leads to worsening of prognosis.[8–10] It is known

Table 2. Laboratory Results and Angiographic Properties of Groups

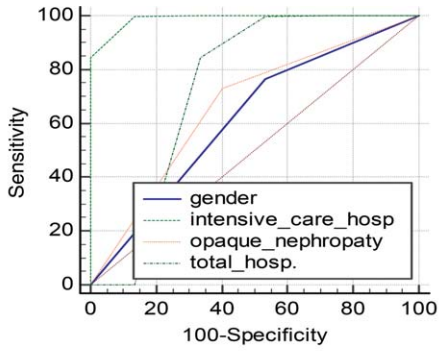
Parameters	Control Group (n = 149)	Study Group (n = 111)	*P*
Glucose	159.9 ± 66.3	167.4 ± 87.5	.660
Urea	34.4 ± 16.7	34.0 ± 16.2	.858
Creatinine	0.8 ± 0.4	0.8 ± 0.5	.424
GFR	93.4 ± 24.6	92.5 ± 25.1	.773
WBC	11.5 ± 4.7	12.0 ± 5.2	.428
HGB	13.3 ± 3.0	13.6 ± 1.7	.447
PLT	245.6 ± 77.4	241.5 ± 68.8	.656
LDL	129.1 ± 39.2	135.7 ± 28.9	.104
HDL	39.7 ± 8.7	40.6 ± 7.1	.107
BNP	2598.4 ± 5067.6	2774.4 ± 5842.8	.796
Ck-MB	30.7 ± 41.5	25.2 ± 40.6	.288
Troponin	18886.0 ± 22176.4	33677.0 ± 56514	.305
Infarct related artery, n (%)			.278
LAD	73 (49)	44 (40)	
CX	25 (17)	25 (22)	
RCA	51 (34)	42 (38)	
Door to balloon, minute	37 (17-62)	39 (19-64)	.342
Procedure time, minute	17 (9-57)	15 (10-40)	.022*
Predilatation, n (%)	109 (73)	68 (61)	.042*
Post-dilatation, n (%)	60 (40)	30 (27)	.026*
Opaque, mL	190 (100-350)	180 (100-260)	.025*
Opaque nephropathy, n (%)	52 (35)	23 (21)	.013*
Hospitalization, hours			
Intensive care	30.0 ± 22.0	35.5 ± 21.6	.048*
Total	74.4 ± 11.2	81.8 ± 16.8	<.001*
Primary end-point, n (%)	11 (7)	4 (4)	.196

Abbreviations: BNP, brain natriuretic peptide; CK, creatine kinase; CX, circumflex artery; GFR, glomerular filtration rate; HGB, hemoglobin; HDL, high-density lipoprotein cholesterol; LAD, left anterior descending artery; LDL, low-density lipoprotein cholesterol; PLT, platelets; RCA, right coronary artery; WBC, white blood cell.
*Statistically significant.

that COVID-19 may cause various symptoms such as classical type 1 MI due to obstructive coronary artery disease, angiographically normal coronaries, myocarditis, or left ventricular dysfunction due to stress cardiomyopathy.[11,12] Among them, patients with ACSs are the most difficult to manage.

With the widespread use of centers where primary percutaneous coronary intervention can be performed, STEMI patients have increased survival and decreased serious complication rates.[13,14] Although the COVID-19 pandemic in nowadays has a negative impact on life, the necessity of the primary intervention for STEMI patients is open to discussion, but it is still the accepted procedure. Vejpongsa et al.[15] point out that influenza and other viral infections are seen simultaneously in 1% of patients with acute MI, and less patients in this group undergo angiography and less of them are revascularized.[16]

Figure 1. ROC curve analysis of variables.



Variable	AUC	SE	95%CI
gender	0.615	0.0680	0.553 to 0.674
intensive_care_hosp	0.989	0.0074	0.967 to 0.998
opaque_nephropaty	0.665	0.0670	0.604 to 0.722
total_hosp.	0.735	0.0969	0.677 to 0.787

Secco et al.[17] suggested that PCI for ACS is often required in Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients and may improve prognosis.[18] In our clinic, which has the capacity to perform invasive procedures for 24 hours, STEMI patients are transferred directly from the emergency department to the angio laboratory, whether or not COVID-19 is suspected, and percutaneous intervention is performed as soon as possible. Considering the pandemic period and before, the lack of a significant difference in the door balloon durations of these patients is the biggest indicator of this. Mahmud et al.[19] pointed out that all patients presenting with STEMI nowadays should be considered COVID-19 positive. Since STEMIs were taken directly to the angiography laboratory, all of them were considered COVID-19 (+) in our study too.

The patients included in this study were taken to the primary PCI catheter laboratory, and the cardiologists who performed the procedure made practices to keep the patient contact as short as possible and to reduce the complex procedure rates. Many studies have shown that viral load is directly proportional to contact time.[20,21] For this reason, it is observed in our study that applications such as pre–post-dilatation, which would prolong the procedure during angiography, decreased in proportion. Similarly, the amount of opaque used is less in patients in the pandemic period in relation to the duration. Consequently, the rate of opaque nephropathy was lower in the study group. We think that the increase in intensive care and service hospitalization times is due to the examinations and consultations that are developed due to the patients' admission during the pandemic process and requested to exclude or confirm the diagnosis of COVID-19.

The fact that no difference was observed in the mortality rates of the patients should be considered as a success of invasive cardiologists even during the pandemic period. The difference in features related to the angio procedure suggests that the simplest is sometimes the best choice.

Limitations

The most important limitation of the study is that it is retrospective and single centered. Since there is no follow-up after discharge, we do not have information about long-term morbidity and mortality. As a result, it is not possible to comment on the medium- and long-term results of the techniques related to angiography, the decrease in pre- and post-dilatation applications.

CONCLUSION

For STEMI patients in the pandemic period, no increase in in-hospital mortality was recorded with the continuation of routine primary PCI application and minor changes in technical practices by the cardiologists who performed angiography.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Adana Health Practice and Research Center (No.: 799/55, date: April 24, 2020).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.Y.; Design - Ö.Ö.A.; Supervision - Ş.D.; Resources - A.Y.; Materials - Ö.Ö.A., Ş.D.; Data Collection and/or Processing - Ö.Ö.A., S.K.; Analysis and/or Interpretation - A.Y., Ö.Ö.A., Ş.D., S.K.; Literature Search - A.Y., Ö.Ö.A., Ş.D.; Writing Manuscript - A.Y.; Critical Review - A.Y., S.K.

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Original Article

Effects of Bilateral Infraorbital–Supraorbital Nerve Block on Postoperative Pain Control and Drug Consumption in Rhinoplasty

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ABSTRACT

Objective: Rhinoplasty is a common procedure performed in plastic surgery. Postoperative pain, edema, and periorbital ecchymosis are the most common acute complications of this surgical procedure. In this study, we aimed to evaluate the postoperative pain and analgesic consumption after rhinoplasty of patients who had bilateral supraorbital and infraorbital nerve block.

Methods: Eighty-four patients who underwent rhinoplasty under general anesthesia, between 17 and 41 years of age, and who underwent intravenous patient-controlled morphine analgesia for postoperative analgesia were included in this study. The cases were divided into two groups: bilateral supra-infraorbital block with intravenous analgesic (Group B) and only intravenous analgesic (Group C). Demographic data, hemodynamic data, operation time, visual analog scale values, patient-controlled analgesia device data, complaints of nausea-vomiting, and antiemetic drug use were recorded.

Results: The hemodynamic data of the cases included in this study were similar ($P > .05$). When compared with Group C, postoperative 1st, 6th, and 24th hour visual analog scale (VAS) scores were found to be significantly lower in Group B ($P < .05$). Morphine consumption at the end of the postoperative 24 hours was found to be significantly lower in Group B compared with Group C ($P < .05$).

Conclusion: In this study, which cases undergoing bilateral supraorbital-infraorbital nerve block and IV morphine was used for postoperative analgesia after rhinoplasty, significant reductions were achieved in the postoperative VAS values and analgesic consumption of the cases where the block was used.

Keywords: infraorbital nerve block, supraorbital nerve block, rhinoplasty, postoperative pain

INTRODUCTION

It is thought that factors such as the degree, location, duration of the surgical intervention, the type of anesthesia, the subjective nature of the pain, the patient's treatment, and the importance attributed to the pain may cause different rates of surgical pain incidence. Whatever the cause, pain is a threat to the organism, and the organism creates a stress response to this situation. In this situation, if the pain, which is considered as a stressor, persists for a long time, physiopathological responses to pain develop in the organism.[1,2] Postoperative pain management is an important part of postsurgical perioperative care. It is known that proper treatment of postoperative pain reduces perioperative morbidity, complications, hospital stay, and costs.[3]

Rhinoplasty is a common procedure performed in plastic surgery. Intravenous (IV) analgesics are frequently used for postoperative pain control in rhinoplasty surgery. In addition, regional nerve blocks and local anesthetic injections are among the options in postoperative pain control.[4–6] Multimodal analgesia applications are frequently preferred in combating acute pain.[7–9]

The use of peripheral nerve blocks for postoperative analgesia has been found to be beneficial for patient recovery and economics. In addition to improvements in pain control, reductions in opioid use can be achieved in many surgical procedures. By reducing the use of analgesic drugs, recovery is supported and the length of hospital stay can be shortened.[10,11]

In this study, it was aimed to compare the postoperative pain and analgesic drug consumption of the patient-controlled IV morphine group and the bilateral supraorbital and infraorbital nerve block (BSIB) groups after the rhinoplasty surgery.

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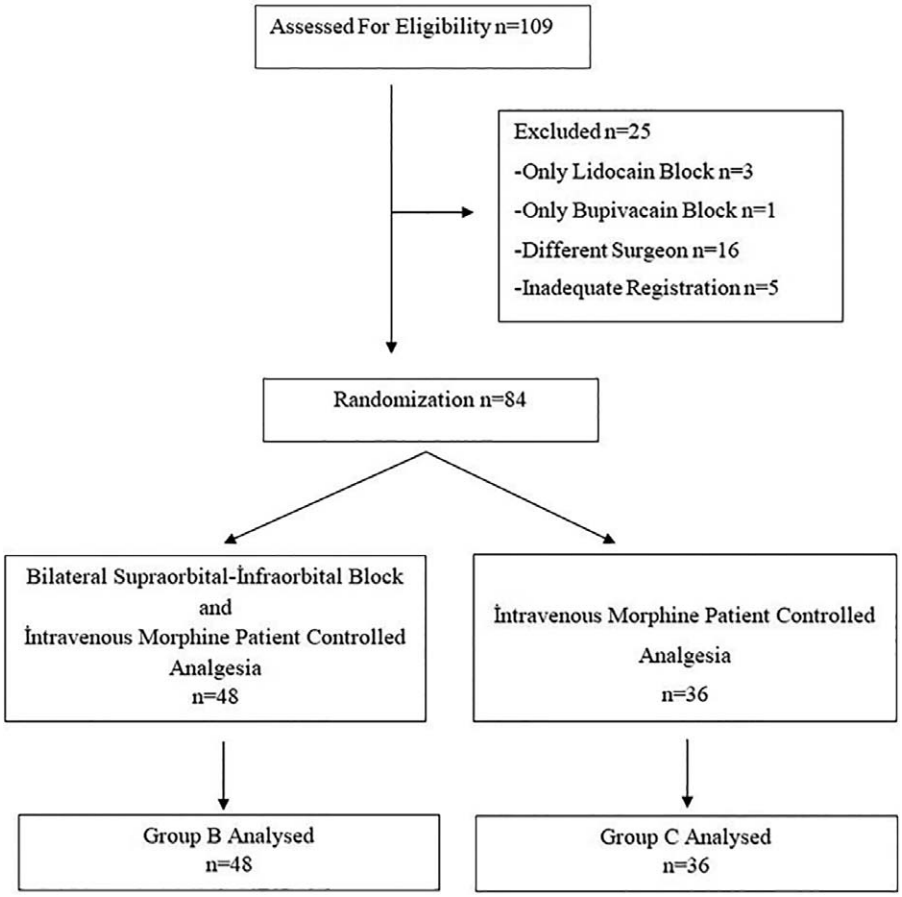
Figure 1. Flow diagram of the study.



METHODS

Setting and Participants

This study was conducted in accordance with the Helsinki declaration after the ethics committee approval (date-number: 2018/17-83116987-577) was obtained. Files of patients who underwent rhinoplasty under general anesthesia between January and December 2018 were reviewed. Information concerning the trial was explained both orally and in a written form to all patients, and a written informed consent form was signed by each patient. Rhinoplasty was performed in all patients using the lateral-medial oblique osteotomy technique. Eighty-four patients, whose physical status was ASA I according to the American Society of Anesthesiology (ASA) classification, between the ages of 17 and 41, and who were followed-up with patient-controlled morphine analgesia, were included in this study. The cases were divided into two groups. According to the postoperative analgesia plan, the groups were determined as BSIB (Group B) and IV morphine (Group C) for postoperative analgesia.

The cases in Group B, in which a local anesthetic mixture including 5 mg bupivacaine and 10 mg lidocaine for a total of 1.5 mL was preferred as local anesthetics, were included in this study. In cases where morphine was used for postoperative analgesia, cases where morphine at a dose of 0.1 mg kg^{-1} was preferred were included in this study. All of the included cases were defined as those who were operated on by the same anesthesiologist and the same surgeon. Cases with disorientation and cooperation, patients with additional systemic disease, regular medication using, and intraoperative additional local anesthetics applying were excluded from this study. In addition, cases with insufficient records, preferred different IV analgesics or local anesthetics, and operated by different anesthesiologists or surgeons were also excluded from this study (Figure 1).

Main Points

- BSIB in rhinoplasty can reduce postoperative pain in the first 24 hours.
- BSIB can reduce the need and consumption of analgesics in the early postoperative period.
- Regional anesthesia techniques can be used effectively in postoperative pain control in accordance with surgery.

Supraorbital and Infraorbital Nerve Blocks

In routine block applications in our clinic, the hemodynamic values (heart rate, systolic blood pressure, diastolic blood pressure, and pulse oximetry) are recorded after the patient is taken

Table 1. Comparison of Demographic Data and Operation Time

	Group B (n = 48)	Group C (n = 36)	*P* Value
Age (mean ± SD)	26.88 ± 5.45	25.67 ± 5.19	.978
BMI (mean ± SD)	20.65 ± 2.80	20.25 ± 2.84	.536
Gender			
Female (n/%)	32/55.2	26/44.8	.586
Male (n/%)	16/61.5	10/38.5	
Operation time (mean ± SD)	91.35 ± 20.57	85.83 ± 19.62	.600

to the operating room. BSIBs are applied before anesthesia induction. A 27-gauge needle is used for the block. For the supraorbital nerve, the supraorbital ridge is palpated, the supraorbital foramen is detected in the medial region, and local anesthetic injection is applied. For the infraorbital nerve, the infraorbital foramen is palpated, and local anesthetic injection is made. Then, anesthesia is induced.

Data Collection and Randomization

Demographic data (age, gender, and BMI), hemodynamic data (basal, postinduction, 15, 30, 45, and 60 minutes, and the end of the operation), operation time, visual analog scale (VAS) values (1st, 6th, and 24th hour), patient-controlled analgesia (PCA) device records (24th hour delivery-morphine consumption amount), complaints of nausea-vomiting, and antiemetic drug use of the patients were recorded.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc.; Chicago, IL, USA) program was used for the analysis of the collected data. Continuous variables obtained were expressed as mean ± SD or number (%). Number and percentage values were used in the presentation of categorical variables. Compliance of the obtained data to normal distribution was checked using the "Kolmogorov–Smirnov test." "Mann–Whitney-U" test was used for the analysis of continuous variables (age, weight, etc.). "Chi-square test" was used to compare the two groups and to examine categorical variables. A *P* value of <.05 was considered significant in the analyzes.

RESULTS

A total of 109 cases were included in the evaluation of the cases. In addition to the three cases using lidocaine only for BSIB for postoperative analgesia, one case using only bupivacaine, 16 cases operated by a different surgeon, and five cases with insufficient file records were excluded from this study. A total of 25 cases were excluded, and 84 cases were included in this study.

The average age of Group B was 26.88 ± 5.45 (n = 48), and it was 25.67 ± 5.19 (n = 36) for Group C. There was no statistical difference between the groups in terms of age, BMI, and sex. Operation time of the groups was 91.35 ± 20.57 minutes in Group B, while it was 85.83 ± 19.62 minutes in Group C, and no statistically significant difference was found between the groups ($P = .60$) (Table 1). When the hemodynamic follow-up values were compared, there was no significant difference between the groups ($P > .05$) (Table 2).

In the comparison of the VAS scores of the 1st, 6th, and 24th hours in the postoperative pain assessment, VAS scores were found to be significantly lower in Group B at all times ($P < .05$) (Table 3). Twenty-four-hour delivery and morphine consumption amount in PCA records were found to be significantly lower in Group B (Table 3). In the postoperative nausea-vomiting comparison, there was no difference between the groups, and antiemetic drugs were administered in all cases ($P > .05$) (Table 3).

DISCUSSION

In this study, which compared the pain scores and analgesic consumption in the first 24 hours of the patients who were used BSIB for postoperative analgesia in rhinoplasty and the patients who received analgesia with IV morphine, it was shown that the patients who underwent block had significant reductions in postoperative VAS values and analgesic consumption.

Postoperative pain management is globally reported to be insufficient.[12,13] After surgical interventions, pain is one of the important parameters affecting patient comfort. Having a comfortable postoperative experience, especially in the early period, increases the comfort and satisfaction of the patients. In addition to regular analgesia in the early period, it is important to perform additional interventions that reduce the need for analgesia and increase patient comfort.[14,15] Szychta et al.[16] stated in their study that patients need analgesics for 3 days after a septorhinoplasty operation. They reported that this pain worsened in the evening, with significantly higher pain scores in the first 3 days postoperatively. They recommended the use of PCA and opioids for pain control.

Various methods have been tried in the perioperative period to prevent postoperative pain in rhinoplasty.[1,2] In rhinoplasty, it has been shown that pregabalin given 1 hour before the operation reduces the postoperative analgesic requirement.[17] Gozeler et al.[18] reported that preoperative single dose IV ibuprofen administration reduced the postoperative fentanyl consumption. Vahabi et al.[19] reported that esmolol infusion reduced

Table 2. Comparison of Hemodynamic Data Over Times

	Heart Rate (Mean ± SD)			Pulse Oximeter (Mean ± SD)			Systolic Blood Pressure (Mean ± SD)			Diastolic Blood Pressure (Mean ± SD)		
	Group B (n = 48)	Group C (n = 36)	*P* Value	Group B (n = 48)	Group C (n = 36)	*P* Value	Group B (n = 48)	Group C (n = 36)	*P* Value	Group B (n = 48)	Group C (n = 36)	*P* Value
Preoperative	81.94 ± 14.62	82.08 ± 14.90	.986	95.88 ± 1.89	95.61 ± 2.10	.783	148.27 ± 18.68	147.53 ± 19.07	.955	81.38 ± 12.91	81.64 ± 9.57	.054
Anesthesia induction	74.31 ± 10.47	72.44 ± 9.30	.619	98.75 ± 1.62	99.19 ± 1.12	.030	109.29 ± 21.88	117.61 ± 18.05	.946	62.67 ± 9.54	64.25 ± 10.85	.483
15 minute after induction	65.46 ± 11.31	68.94 ± 12.17	.747	98.79 ± 1.35	98.94 ± 1.19	.554	116.13 ± 19.04	112.28 ± 28.92	.082	66.38 ± 15.15	65.25 ± 12.75	.267
30 minute after induction	64.98 ± 12.00	66.69 ± 10.05	.494	98.50 ± 1.31	98.75 ± 1.34	.933	123.00 ± 23.25	118.44 ± 29.94	.307	69.48 ± 15.57	69.19 ± 13.30	.487
45 minute after induction	63.88 ± 9.55	65.61 ± 9.48	.812	98.63 ± 1.28	98.44 ± 1.38	.505	121.44 ± 20.20	120.47 ± 21.75	.276	67.21 ± 12.91	66.72 ± 14.68	.718
60 minute after induction	62.54 ± 9.74	64.19 ± 10.16	.735	98.71 ± 1.03	98.39 ± 1.38	.094	115.85 ± 28.05	117.25 ± 27.46	.692	68.60 ± 15.47	66.53 ± 16.09	.920
End of the surgery	60.31 ± 8.68	60.94 ± 8.88	.818	98.63 ± 1.27	98.97 ± 1.11	.156	114.19 ± 25.53	122.14 ± 25.14	.742	65.98 ± 11.44	70.42 ± 14.37	.106

Table 3. Comparison of Pain Values and Drug Consumption Amounts of the Groups

	Group B (n = 48)	Group C (n = 36)	*P* Value
Visual analog scale (VAS)			
First hour (mean ± SD)	2.21 ± 0.87	8.06 ± 1.07	**<.001***
Sixth hour (mean ± SD)	2.75 ± 0.94	8.28 ± 1.16	**<.001***
Twenty–fourth hour (mean ± SD)	4.00 ± 1.22	8.95 ± 1.15	**<.001***
Patient control analgesia (PCA) records			
Delivery (count) (mean ± SD)	3.88 ± 2.47	17.17 ± 4.98	**<.001***
Morphine consumption (mg) (mean ± SD)	2.60 ± 1.37	11.78 ± 2.80	**<.001***
Postoperative nausea and vomiting			
Positive (n/%)	19/50	19/50	.229
Negative (n/%)	29/63	17/37	

* statistically significant difference ($P < .05$)

postoperative pain in rhinoplasty surgeries performed with propofol and remifentanil infusion. It has been shown that packs impregnated with local anesthetic reduce postoperative pain.[4]

Regional nerve blocks and local anesthetic applications have also taken their place among the methods used in postoperative pain control in nasal surgeries. Higashizawa and Koga[20] reported that infraorbital nerve block reduces anesthetic drug consumption and postoperative pain in endoscopic nasal surgeries under general anesthesia.[20] Similarly, it reduces postoperative opioid consumption in children and also reduces pain.[5] In the comparison of the patients who underwent total nasal block and central facile block, a significant reduction in pain was observed in the central facile block on the 1st and 2nd days compared to the total nasal block and control groups. The more effective total nasal block is attributed to the infraorbital nerve block, which is not present in facile block.[6]

Postoperative pain levels are at their maximum in the first 24 hours of surgery.[1,2] In the previous studies, first day of postoperative pain after rhinoplasty investigated different time intervals.[19,21–23] In this study which pain control was performed most frequently, time intervals were planned as 5th, 15th, 30th minutes and 1st, 2nd, 4th, 6th, 8th, 16th, and 24th hours.[21] In data collection, it was observed that in line with previous studies, postoperative pain controls in the first 24 hours were obtained regularly in the 1st, 6th, and 24th hours. In our study, significant decreases were found in the VAS values of the block group at all time intervals. When the 24th hour PCA records were examined, a significant decrease was observed in both delivery and morphine consumption values in cases where block was applied. These findings show that postoperative opioid need and opioid consumption decreased with nerve block.

"Postoperative nausea and vomiting" (PONV) is defined as nausea, retching, or vomiting within 24-48 hours after surgery. When no prophylaxis is applied, it is seen in 20-30% of all patients undergoing surgery. It is seen in 70-80% of patients with drugs used for anesthesia and analgesia, and surgical risk factors.[24] Anesthetic factors that play a role in the development of PONV are inhalation anesthetic use, duration of anesthesia, postoperative opioid use, and nitrite oxide.[25] It has been reported that opioids used in the postoperative period increase the risk of PONV, depending on the dose.[26] In this study, because the use of morphine was significantly higher in Group K, it can be expected that the symptoms of nausea and vomiting would be more. However, there was no significant difference between the groups in terms of nausea and vomiting. This has been attributed to the use of prophylactic antiemetics in all cases.

This study has some limitations. It is a retrospective study. Data in the first 24 hours were evaluated in this study. Postoperative pain levels are expected to be at the highest level in the first 24 hours, and with the use of multimodal analgesia, pain levels and analgesic consumption after 24 hours are expected to be lower.

CONCLUSION

In conclusion, bilateral infraorbital-supraorbital nerve block application in rhinoplasty provided significant pain relief for the first 24 hours. Thus, it reduces the need and consumption of analgesics in the early postoperative period. Randomized controlled studies are needed to evaluate local anesthetic preference and dose.

Ethics Committee Approval: Ethical committee approval was received from the Gaziosmanpaşa University (date-number: 2018/17-83116987-577).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Original Article

Evaluation of Oxidative DNA Damage and Thiol–Disulfide Homeostasis in Patients with Aortic Valve Sclerosis

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ABSTRACT

Objective: The free radicals in the organism are important events in aortic valve sclerosis (AVS) because they cause conditions such as cell proliferation, growth arrest, and/or apoptosis and oxidation of low-density lipoprotein (LDL). This study was to evaluate DNA damage in patients with AVS and its relationship with thiol–disulfide homeostasis.

Methods: Forty AVS subjects (30 female) were enrolled in this study and compared with control group. The diagnosis of AVS was made by comprehensive echocardiography. Biochemical parameters were measured in the sera of the control and AVS subjects.

Results: In the AVS group, total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), disulfide, total thiol, natural thiol, disulfide/total thiol, disulfide/natural thiol, and oxidative 8-OH deoxyguanosine levels were significantly lower than those of the control group, whereas natural thiol/total thiol levels were significantly found to be higher. In addition, there was a statistically negative correlation between OSI and TAS in patient and control groups, and a positive correlation between OSI and TOS and natural and total thiol parameters. The results show DNA damage and impaired thiol-disulfide homeostasis.

Conclusion: Our findings suggest that increased oxidant stress may signify an important point in the onset and progression of AVS. Therefore, adding antioxidants to treatment may shed light on new therapeutic targets for reinforcing the antioxidant system, slowing or even stopping aortic valve stenosis.

Keywords: Reactive oxygen species, oxidative stress, oxidative DNA damage, free radicals, antioxidants, thiol-disulfide homeostasis

INTRODUCTION

Aortic valve sclerosis (AVS) is defined as thickening and calcification of aortic valve patients in cases where ventricular outflow is not obstructed.[1–3] AVS is the most common valve disease in developed countries and is also common in western countries. It is found in about 25% of people in the 65 age group and increases to 50% in the 80 age group. Recent studies show that aortic valve disease is common in the US adult population and causes more than 28,000 deaths and 48,000 hospitalizations per year.[4,5] Most studies have proved that patients with AVS have an augmented incidence of cardiovascular events and mortality.[6,7] AVS developing approximately takes six decades. Then, it takes around one decade for a patient to progress aortic valve stenosis. There is also no randomized controlled trial on drug therapy in aortic sclerosis. Therefore, no medical interventions are able to delay or stop the AVS progression.[8]

Reactive nitrogen species (RNS), reactive oxygen species (ROS), and other radicals are produced as a normal result of metabolism.[9–11] When ROS and RNS are overproduced, they cause oxidative and nitrosative stress, respectively.[12–14] In many studies, the formation of overactive ROS has been reported to cause cellular damage and atherogenesis. In addition to the deleterious effects of ROSs, they are also expressed to be involved in various cell processes involving initiation of cell proliferation and gene expression, growth arrest, hypertrophy, and induction of apoptosis.[15–18] However, research has suggested that ROS/RNS can have some detrimental effects on DNA and, indeed, trigger chromosomal aberrations, DNA strand breaks, and, consequently, DNA damage from endogenous free radical attacks, contributing to many diseases.[19–22] Some studies state that an important feature of atherosclerotic plaques (APs) is oxidative DNA damage.[17,23]

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Thiols, which play in redox homeostasis and are composed of functional sulfhydryl groups, are important molecules of the oxidant/antioxidation system. In living systems, the thiol representing the reduced state and the disulfide groups representing the oxidized state are regularly converted into each other to maintain stability between the thiol and disulfide groups. Dynamic thiol/disulfide balance is defined as a new oxidative stress (OS) marker, and it has been stated in studies that it plays a role in the pathophysiology of a lot of diseases, including diabetes and cardiovascular disorders.[24,25]

To our best knowledge, there are no studies researching thiol-disulfide homeostasis in patients with AVS. Therefore, we aimed to evaluate serum thiol/disulfide status, total oxidant status (TOS), total antioxidant status (TAS), and the levels of 8-OH deoxyguanosine (8-OHdG) in these patients and search the role of active stress pathways in the pathogenesis of AVS and whether the results obtained correlated with disease severity.

METHODS

Study Population

All subjects were included in the study after obtaining their informed consent. A total of 80 subjects, 40 patients (30 females and 10 males) with AVS and 40 controls of healthy volunteers, were included in this study. The diagnosis in these patients was made by a cardiologist based on echocardiography scans. Echocardiographic evaluation was performed to determine whether the control group had heart pathology. The subjects in the control group had normal aortic valve tips and did not have any cardiovascular disorders or other diseases (such as liver, kidney disease, diabetes, hypertension, and cancers). Pregnant patients and individuals with severe diseases (such as renal dysfunction, lung disease, blood diseases, rheumatoid arthritis patients, cancer, liver disease, congenital heart disease, and other heart diseases) were not included in the study to prevent possible effects on serum biochemical parameters. This study was approved by Gaziantep University Clinical Research Ethics Committee with a protocol no. 2018/195 on November 7, 2018.

Echocardiography

The standard for diagnosing AVS was depended on the hemodynamic and morphologic findings in the echocardiographic study in the aortic valve by the wall thickness of a given hump (2-6 mm at minimum one abnormal leaflet per valve), with a transaortic flow rate of <2.5 m s^{-1}.

Biochemical Analysis

TOS, TAS, thiol-disulfide levels, and the 8-OHdG, the marker of DNA damage, from the venous blood samples taken from the control and patient groups were measured in xxx University Medical Faculty Hospital medical biochemistry research laboratory. To obtain serum, blood samples were centrifuged at 3,500 rpm for 8 minutes. Serum samples obtained were placed into ependrof tubes and stored at –80°C until analysis.

Total Oxidant Status Assay

TOS was determined as described by Erel.[26] TOS measurement was performed using an automated analyzer (Beckman Coulter AU480 Chemistry Analyzer) fully automatic TOS kit (Rel Assay DC, Gaziantep, Turkey). Results are expressed in μmol H_2O_2 equiv. L^{-1}.

Total Antioxidant Status Assay

TAS was determined as described by Erel.[27] TAS measurement was performed using a fully automatic RAS kit in the Beckman Coulter AU480 Chemistry autoanalyzer (Rel Assay DC, Gaziantep, Turkey). Results are expressed in mmol Trolox equiv. L^{-1}. Oxidative stress index (OSI) was calculated by using TOS and TAS values. First, the TAS unit was turned into μmol L^{-1}. Then, TOS values were divided by TAS values and multiplied by 100. The resulting ratio was expressed as OSI.

Serum Thiol-Disulfide Measurement

In this method, disulfide, total thiol, and native thiol concentrations were detected. Then, other parameters were calculated, which expressed as μmol L^{-1}.[28]

Serum 8-OH Deoxyguanosine Measurement

8-OHdG levels were determined by ELISA method, which expressed as ng mL^{-1}.

Statistical Analyses

Data analysis and receiver operating characteristic (ROC) curve analysis were performed using Statistical Package for Social Sciences for Windows, version 11.5 (SPSS Inc.; Chicago, IL, USA). The Shapiro-Wilk test was used to determine whether continuous variables were normally distributed. Results obtained were expressed as mean ± SD. Differences between the groups in the normally distributed variables were analyzed using independent sample's T test. The Mann–Whitney U test was used to analyze the differences between the non-normal distribution data. In the correlation analysis, Pearson correlation analysis was used for normal variables and Spearman correlation analysis for non-normal distribution. *P* values $<.05$ were considered statistically significant.

RESULTS

Samples were run duplicate, and their means were used for statistical evaluations. TAS, TOS, OSI, thiol/disulfide parameters, and 8-OHdG, which are indicators of oxidative DNA damage, levels were measured in the sera of patients in AVS and control groups (Tables 1-3 and Figure 1). In the AVS group, TOS, TAS, OSI, total thiol, native thiol, disulfide, disulfide/total thiol, disulfide/native thiol, and 8-OHdG levels were found to be significantly lower when compared with the control group. However,

Main Points

- Free radicals are produced as a result of normal metabolism.
- Excessive free radical production causes oxidative/nitrosative stress and plays a role in the pathogenesis of many diseases.
- The addition of antioxidants to the treatment makes a great contribution to the prevention of oxidative/nitrosative stress.
- Adding antioxidants to the treatment could shed light on new therapeutic goals for slowing or even stopping aortic valve stenosis.

Table 1. Mean ± SD Values of Biochemical Parameters Measured in Patient and Control Groups

Parameters	Control Group (n: 40) (Mean ± SD)	Patient Group (n: 40) (Mean ± SD)	*P* Values
Native thiol (μmol L^{-1})	300.19 ± 18.12	289.72 ± 21.64	.05
Total thiol (μmol L^{-1})	323.79 ± 18.27	309.96 ± 24.87	.01
Disulde (μmol L^{-1})	11.80 ± 1.86	10.12 ± 3.54	.01
Disulde/native thiol (%)	3.94 ± 0.68	3.48 ± 1.17	.05
Disulde/total thiol (%)	3.65 ± 0.58	3.23 ± 1.01	.05
Native thiol/total thiol (%)	92.69 ± 1.16	93.52 ± 2.03	.05
Total antioxidant status (mmol Trolox equiv. L^{-1})	1.58 ± 0.2	1.49 ± 0.17	.05
Total oxidant status (μmol H_2O_2 equiv. L^{-1})	14.35 ± 0.59	4.77 ± 0.56	.01
Oxidative stress index (arbitrary unit)	0.24 ± 0.05	0.31 ± 0.06	.01

The results obtained in mean and standard deviation values were compared between the two groups. $P < .05$ was considered statistically significant.

Table 2. Correlation Analysis in the Patient Group

		TOS	OSI	Native Thiol	Total Thiol	Disulfide	8-OHdG
TAS	r	n.c.	**−0.512****	n.c.	n.c.	n.c.	n.c.
	P		.001				
	n		40				
TOS	r		**−0.745*****	n.c.	n.c.	n.c.	n.c.
	P		.000				
	n		40				
OSI	r			n.c.	n.c.	n.c.	n.c.
	P						
	n						
Native thiol	r				**0.963****	0.326*	n.c.
	P				.000	.04	
	n				40	40	
Total thiol	r					0.569***	n.c.
	P					.000	
	n					40	

*$P = .04$
**$P < .001$
***$P < .000$

native thiol/total thiol levels were found to be statistically higher than the control group. ROC analysis was used to determine the predictive threshold of serum TOS, TAS, OSI, and 8-OHdG levels (Figure 2).

In the correlation analysis, there was a statistically significant negative correlation between TAS and OSI in patient and control groups and positive correlations between TOS and OSI and total and native thiol parameters (Figures 3 and 4).

Table 3. Correlation Analysis in the Control Group

		TOS	OSI	Native Thiol	Total Thiol	Disulfide	8-OHdG
TAS	r	n.c.	**-0.623*****	n.c.	n.c.	n.c.	n.c.
	P		0.000				
	n		40				
TOS	r		**0.805*****	n.c.	n.c.	n.c.	n.c.
	P		0.000				
	n		40				
OSI	r			n.c.	n.c.	n.c.	n.c.
	P						
	n						
Native thiol	r				**0.979*****	n.c.	n.c.
	P				0.000		
	n				40		

****P* < .000, n.c: No correlation

Figure 1. Mean ± SD of 8-OHdG in patients with aortic valve sclerosis and control groups.

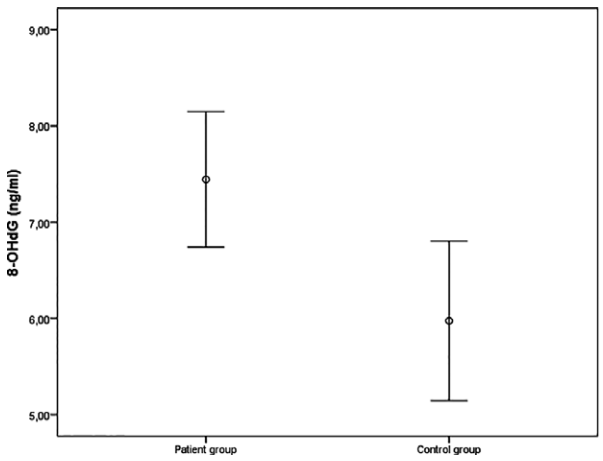
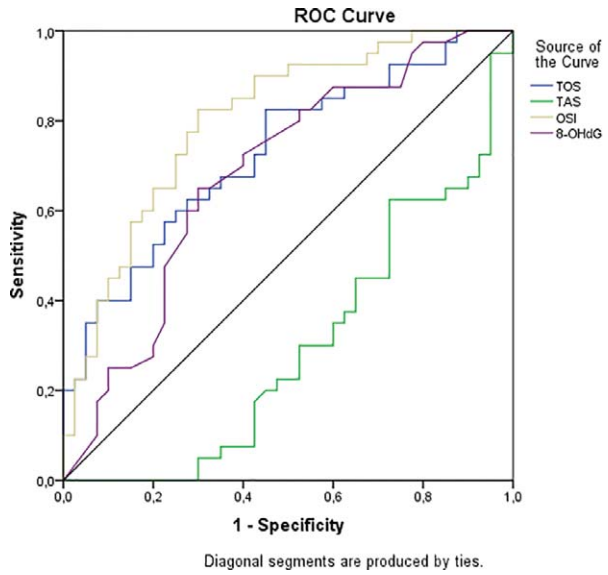


Figure 2. ROC curve analysis showing serum TAS, TOS, OSI, and 8-OHdG in the aortic valve sclerosis group.



The mean descriptive data of the patient and control groups are given in Table 4. Body mass index (BMI) in females in the AVS patient group was significantly higher than the control group ($P = .003$), whereas there was no difference in men. High blood pressures were detected in both genders in the AVS patient group compared with the healthy control group ($P < .05$). In addition, while 42% of the AVS patient group had diabetes, none of the control group had diabetes. In addition, there was no significant difference in diabetes prevalence between different genders in the AVS patient group ($P > .05$) (see more detail in Table 4). The ages of the individuals in the control group ranged from 42 to 65 years, while the age of the individuals in the AVS group was between 39 and 65. In addition, BMI was found to be higher in the patient group compared with the control group (see more detail in Table 5).

DISCUSSION

With increasing evidence of a direct role of OS-induced DNA damage in the experimental model of atherosclerosis, a direct mechanism has been proposed to define the role of DNA

Figure 3. Correlation between total antioxidant status and oxidative stress index in aortic valve sclerosis group.

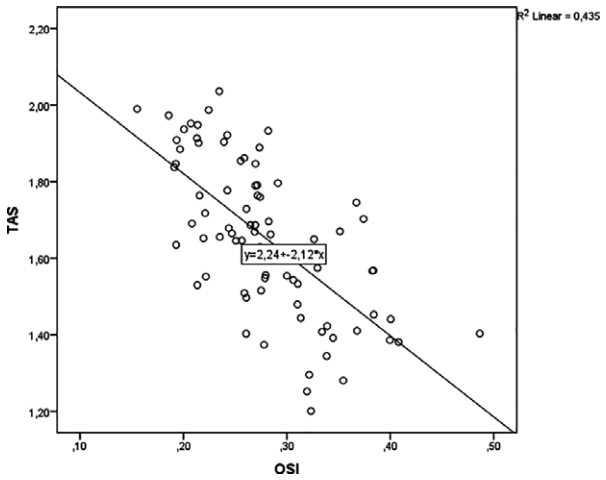


Figure 4. Correlation between total oxidant status and oxidative stress index in aortic valve sclerosis group.

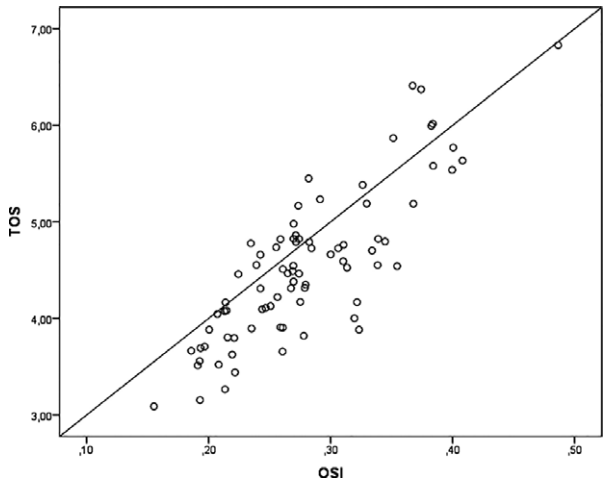


Table 4. Descriptive Analyses of the Study Groups

	Gender	Patient (Mean ± SD)	Control (Mean ± SD)	*P*
Age	Female	56.6 ± 7.6	57.4 ± 7.0	.676
	Male	56.8 ± 6.2	53.4 ± 7.5	.287
	Total	56.6 ± 7.2	56.4 ± 7.3	.878
BMI	Female	34.3 ± 6.5	29.4 ± 5.8	.003
	Male	28.7 ± 2.9	28.7 ± 3.4	.992
	Total	32.9 ± 6.3	29.2 ± 5.3	.006
Systolic blood pressure (mmHg)	Female	145.1 ± 15.9	121.7 ± 9.0	.000
	Male	136.7 ± 15.3	120.0 ± 8.2	.007
	Total	142.9 ± 16.0	121.3 ± 8.7	.000
Diastolic blood pressure (mmHg)	Female	74.5 ± 11.7	64.7 ± 7.8	.000
	Male	72.3 ± 9.6	63.8 ± 5.9	.028
	Total	74.0 ± 11.1	64.5 ± 7.3	.000

BMI, body mass index.

Table 5. Descriptive Analyses of the Study Groups

	n	Minimum	Maximum	Mean	SD
Age (years)	80	39.0	65.0	56.6	7.2
BMI (kg m^{-2})	80	21.1	54.6	31.1	6.0
Systolic blood pressure (mmHg)	80	108.0	168.0	132.13	16.8
Diastolic blood pressure (mmHg)	80	54.0	99.0	69.2	10.5

damage in the development of cardiovascular diseases.[17,29] It is now known that aortic valve stenosis is the final stage of a disease that develops from microscopic early alterations to aortic sclerosis and then to severe bio-mineralization in a subset of patients.[29,30] In order to influence the progression of the transition from sclerosis to stenosis, it is necessary to know the earliest stages of the disease, so that the effects of directed therapy on the microscopic processes in the valve patients can be measured.[29,31] Despite best efforts, progress in understanding, diagnosing, and treating calcific aortic valve disease has prevented in vivo measurement of dynamic molecular events associated with early calcific changes in the valves.[29,32] In spite of the high prevalence of aortic sclerosis, little is known about its developmental stages and pathogenetic mechanisms. The present study provides several new ideas about pathogenesis and progression of AVS.

First, increased oxidant stress and impaired thiol-disulfide homeostasis in AVS patients may cause increased production of ROS as the result of the reduced antioxidant defense system, causing DNA damage (Table 1 and Figures 1-4). However, the oxidative DNA damage caused by the free radical attack in these patients remains a weakly studied area.[29] Free radicals are produced continuously as a result of normal metabolism. In living organisms, excessive ROS/RNS production and inadequate and/or disruption of the enzymatic and nonenzymatic antioxidant defense system that neutralizes the free radicals formed cause oxidative and nitrosative stress, respectively. Since OS and one of its consequences, DNA damage, play a vital role in the pathogenesis of many illnesses,[33–35] it is important to understand this and to clarify how improvements are needed in this area.

In contrast, low/medium concentrations oxidative/nitrosative of ROS/RNS have beneficial effects on living organisms. They include physiological roles in cellular responses to noxia, as, for example, in defence against infectious agents, in the function of many cellular signaling pathways, and the induction of a mitogenic response.[36] ROS/RNT overproduction causes significant injury to cell structures including membranes and lipids, DNA, and proteins.

Indeed, studies have suggested that ROS/RNS can trigger chromosomal aberrations extensive, DNA strand breaks, and DNA damage, and that important damage to DNA from endogenous free radical attacks contributes to cancer pathology and various neurodegenerative diseases.[17] In our study, increased DNA damage was detected in the serum of patients with AVS. This finding supports the assumption that oxidative tissue damage is exacerbated during the formation of stenosis. 8-OHdG is an important DNA damage marker that occurs in the presence of oxidative/nitrosative stress in mammalian DNA.

Thiol groups, which have an important share in the antioxidant activity of the blood, and other antioxidants play an important role in preventing oxidative damage to biomolecules.[37] Reactions resulting in thiol–disulfide exchange have important roles in biology. It has long been thought that these reactions have only a protein stabilizing structural purpose, but it is now clear that many enzymes are also responsible for the various dynamic functional properties. The oxidized state as disulfide groups and reduced state as thiol are regularly converted into one another as a result of normal metabolism, maintaining stability between the thiol and disulfide groups. The dynamic thiol/disulfide balance has been identified as a novel OS marker and has been shown to participate in antioxidant protection, detoxification, and apoptosis.[38,39] In this study, we demonstrated that thiol/disulfide homeostasis varies against to thiol concentrations in patients with AVS. There was a statistically important decrease in the other thiol and disulfide parameters in the patient group except for the native thiol/total thiol ratio. This causes a significant decrease in the antioxidant defense system and an augment in oxidant stress.

Reduction in TAS and increased OSI and TOS in the patient group is an important evidence of the presence of OS. In addition, a statistically significant negative correlation between OSI and TAS and a positive correlation between TOS and OSI support our hypothesis. TAS measures the cleaning capacity of free radicals of the extracellular antioxidant system consisting of sulfhydryl groups (mostly albumin), phenol compounds, vitamins A, C, and E, and proteins. TAS is an important reflection of the residual antioxidant status after cleaning of ROS/RNS. DNA damage is associated with OS.[40] Therefore, this suggests that DNA damage may be due to insufficient antioxidant capacity and excessive ROS/RNS formation that contribute to the pathogenesis of the disease in patients with AVS. For this reason, the finding supports the hypothesis of OS involvement in the disease process.

Demirdağ et al.[19], in a study in which they measured both TAS and TOS levels in plasma and human APs, found that TAS and TOS levels in plasma were significantly increased compared to APs. They showed that the severity of atherosclerosis was significantly related to plasma antioxidant levels rather than tissue levels. They suggested that the improvement of plasma TAS may represent an important target for the treatment of atherosclerosis disease. In another study by Klimiuk et al.,[37] it is emphasized that enzymatic and nonenzymatic antioxidant defense system defects in patients with chronic heart failure, and oxidative damage occurs in proteins and lipids in plasma/erythrocytes. They note that redox homeostasis disorders often worsen with the progression of heart failure, and some parameters of OS in saliva can be used as potential diagnostic biomarkers.

Limitations

The most important limitations are the limited number of patients, and the fact that it is performed as a single center study. A multicenter experiment will more accurately reflect real-world data. Finally, a prospective follow-up of these patients may show different rates of progression to clinical aortic stenosis among patients with normal and low levels of these parameters.

CONCLUSION

This is the first research to detect impaired thiol/disulfide homeostasis in patients with AVS. We have also detected augmented OS and DNA damage and decreased antioxidant capacity in these patients. Our findings suggest that increased

oxidant stress might represent a significant point in the onset and progression of AVS. Therefore, adding antioxidants to the treatment may shed light on new therapeutic targets for the recovery of thiol disulfide balance, slowing or even stopping AVS. However, more extensive further studies on the subject were needed.

Ethics Committee Approval: Ethical committee approval was received from the Gaziantep University Clinical Research Ethics Committee (protocol no. 2018/195 on November 7, 2018).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.Y., M.S., S.T.; Design - M.S., S.T.; Supervision - S.T.; Materials - A.Y., M.S., H.A.-T.; Data Collection and/or Processing - A.Y., H.A.-T., H.U.; Analysis and/or Interpretation - H.U., S.T.; Literature Search - M.S., F.M.E.; Writing Manuscript - S.T.

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

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Erratum

In the article by Karslıgil and Akdoğan, entitled "COVID-19 Seroprevalence among Healthcare Workers in a University Hospital in Southeastern Turkey" that was published in the June 2021 issue of the European Journal of Therapeutics (Eur J Ther; 27 (2): 106-112, DOI: 10.5152/eurjther.2021.20106), the authors declared that they erroneously forgot to add the financial support of the study and requested a correction.

Author's correction request were evaluated and accepted by the Editorial Board. Thus, the article has been corrected accordingly and updated in the journal's archive. You may access the updated article via the link below.

https://eurjther.com/en/covid-19-seroprevalence-among-healthcare-workers-in-a-university-hospital-in-southeastern-turkey-162638