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EDITORIAL

EDİTÖRYAL

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Transcranial Magnetic stimulation in Neurodegenerative Diseases: Basics and Clinical Applications

Nörodejeneratif Hastalıklarda Transkraniyal Manyetik Uyarım: Temeller ve Klinik Uygulamalar

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ABSTRACT

Transcranial Magnetic Stimulation (rTMS) non-invasively modulates brain networks via stimulating relevant brain regions responsible for motor and cognitive functions. However, replicating human and animal data suggests the therapeutic role of repetitive transcranial magnetic stimulation (rTMS) in many neurological diseases. In this paper, we evaluate the role of rTMS on the network neuroplasticity and neuroprotective pathways, including especially the Brain-Derived Neurotrophic Factor (BDNF), which mediates the pro-cognitive and neuroprotective effects of rTMs, suggesting that rTMS is a potential neuroprotective and pro-cognitive therapy.

Keywords: Transcranial Magnetic Stimulation; Neuroprotection; Neurological Diseases; Neuroplasticity; BDNF; Alzheimer'Disease; Parkinson's Disease

ÖZ

Transkraniyal Manyetik Stimülasyon (rTMS), motor ve bilişsel işlevlerden sorumlu ilgili beyin bölgelerini uyararak beyin ağlarını non-invaziv olarak modüle eder. Bununla birlikte, insan ve hayvan verilerinin kopyalanması, birçok nörolojik hastalıkta tekrarlayan transkraniyal manyetik stimülasyonun (rTMS) terapötik rolünü ortaya koymaktadır. Bu yazıda, özellikle rTM'lerin bilişsel ve nöroprotektif etkilerine aracılık eden Beyinden Türetilmiş Nörotrofik Faktör (BDNF) dahil olmak üzere, rTMS'nin ağ nöroplastisitesi ve nöroprotektif yolaklar üzerindeki rolünü gözden geçirdik. BDNF rTM'lerin bilişsel ve nöroprotektif etkileri, rTMS'nin potansiyel bir nöroprotektif ve pro-bilişsel terapi olduğunu düşündürmektedir.

Anahtar Kelimeler: Transkraniyal Manyetik Uyarım; Nöroproteksiyon; Nörolojik Hastalıklar; Nöroplastisite; BDNF; Alzheimer hastalığı; Parkinson hastalığı

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Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive electromagnetic stimulation procedure applied to the skull surface of the patient, which induces a secondary electric field that stimulates relevant brain regions based on magnetic fields1. Therefore, with the advancement of new techniques, transcranial magnetic stimulation has become a preferred method in many neurology disciplines2-4, especially when it comes to network-based neuroprotection approaches in humans and animals.

Basics and Clinical Application

Despite some differences in its application procedures, such as single-pulse TMS and repetitive TMS (rTMS), which are consisting single-pulse stimulation and a series of repetitive

pulses, respectively, both procedures modify the network properties of many neurological diseases, especially neurodegenerative diseases, such as Alzheimer's Disease and Mild Cognitive Impairment 5. Beyond that, TMS has also treat several psychiatric diseases while it has been an FDA approved anti-depressant therapy in the United States since 20085-6.

Although different frequencies of rTMS have divergent effects showing increased and decreased motor excitability when applied at High (> 5 Hz)and low –frequencies rTMS (< 5 Hz) 2, respectively, many experimental studies have revealed that TMS might exert a preclinical neuroprotective and neuroplasticity modifying effect in several studies2-4. A good example is that rTMS could modify clinical network and neurochemical parameters in many animal and human studies. In addition to some cognitive networks, these parameters include some critical neuroprotective molecules, including especially the BDNF. BDNF is a well-known neuroprotective molecule that exerts significant pro-cognitive and neuroprotective properties7-8. Furthermore, it also induces synaptogenesis which is hypothesized to mediate the neuroprotective and anti-depressant effect of rTMS2,7-8. Also, with its cognitive side effect profile, rTMS might be a suitable option in neurodegenerative diseases characterized by cognitive impairment such as Alzheimer's Disease5,8,9 and Parkinson's Disease5,10

It should also be mentioned that with the proven role of neurodegeneration in many neurodegenerative diseases, rTMS might be a novel tool with its additional neuroprotective and pro-cognitive effects. Thus there are rapidly replicating evidence showing the pro-cognitive and neuroprotective role of rTMS5-10.

Conclusion

TMS is a suitable non-invasive stimulation method for many neurological diseases. Beyond its well-accepted working principles, it can also lead to distant central nervous system effects, including the modulation of molecules and networks responsible for neuroprotection and cognition. Therefore, there is an unmet need for additional human clinical trials to confirm its well-known neuroprotective effects in experimental studies, which could be a game-changer therapy option in human neurodegenerative diseases, primarily are characterized by cognitive dysfunction.

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RESEARCH ARTICLE

ARAŞTIRMA

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Systemic immune-inflammation index and high-sensitivity cardiac troponin T in acute coronary syndromes

Akut koroner sendromlarda sistemik immün-inflamasyon indeksi ve yüksek duyarlılıklı kardiyak troponin T

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ABSTRACT

Aim: Acute coronary syndromes (ACSs) are classified as ST-segment elevated myocardial infarction (STEMI), non-ST-segment elevated myocardial infarction (NSTEMI) and unstable angina pectoris (USAP). Cardiac troponins constitute the cornerstone biomarkers for the laboratory diagnosis of ACS. In this study, we aimed to investigate whether systemic immune-inflammation index (SII) is associated with peak cardiac troponin T (TnT) levels in ACS.
Methods: Consecutive patients with ACS whose coronary angiography was performed were included in the present study (n=397). Admission SII was determined as platelet count x neutrophil count/lymphocyte count. Serum levels of cardiac enzymes, including high-sensitivity TnT and creatine kinase-myocardial band (CK-MB), were measured at the time of admission and repeated daily during patients' hospital stay.
Results: Patients were categorized as namely STEMI (n=92) and NSTEMI/USAP (n=141). The findings obtained in this study showed that the median of SII levels was higher in STEMI than NSTEMI/USAP at a significant level. Correlation analysis of SII with various clinical and laboratory parameters demonstrated a significant correlation with C-reactive protein, peak CK-MB (r=0.52, p<0.001), peak TnT (r=0.49, p<0.001) and left ventricular ejection fraction (r= -0.48, p<0.001). Multivariate linear regression analysis identified age and log-SII (Beta Coefficient: 1.29, 95% Confidence Interval: 0.93-1.66, p<0.001) as independent predictors of peak TnT levels.
Conclusion: SII is an independent predictor of peak TnT levels and significantly correlates with peak CK-MB levels in patients with ACS. SII significantly and inversely correlates with left ventricular systolic functions.

Keywords: Acute coronary syndrome, inflammation, systemic immune-inflammation index, troponin

ÖZ

Amaç: Akut koroner sendromlar (AKS), ST-segment yükselmeli miyokard enfarktüsü (STEMI), non-ST-segment yükselmeli miyokard enfarktüsü (NSTEMI) ve kararsız angina pektoris (USAP) olarak sınıflandırılır. Kardiyak troponinler AKS laboratuvar tanısı için temel biyolojik belirteçleri oluşturur. Biz bu çalışmada sistemik immün-inflamasyon indeksinin (SII) AKS' de zirve kardiyak troponin T (TnT) seviyeleri ile ilişkisini araştırmayı amaçladık.
Yöntem: Koroner anjiyografi yapılan AKS hastaları ardışık olarak çalışmaya dahil edildi (n=397). Başvuru anındaki SII değeri, trombosit sayısı x nötrofil sayısı / lenfosit sayısı olarak belirlendi. Yüksek duyarlılıklı TnT ve kreatin kinaz-miyokardiyal bandı (CK-MB) içeren serum kardiyak enzim seviyeleri başvuru sırasında ölçüldü ve ölçümler hastaların hastanede kaldıkları süre boyunca günlük olarak tekrarlandı.
Bulgular: Hastalar STEMI (n = 92) ve NSTEMI/USAP (n = 141) olarak kategorize edildi. SII ortanca değerleri STEMI grubunda NSTEMI/USAP grubundan anlamlı düzeyde daha yüksekti. SII' nin çeşitli klinik ve laboratuvar parametreleriyle yapılan korelasyon analizinde C-reaktif protein, zirve CK-MB (r = 0.52, p <0.001), zirve TnT (r = 0.49, p <0.001) ve sol ventrikül ejeksiyon fraksiyonu (r =-0.48, p <0.001) ile anlamlı bir korelasyon gösterdiği tespit edildi. Çok değişkenli doğrusal regresyon analizi yaş ve log transforme-SII' yi (Beta Katsayısı:1.29, % 95 Güven Aralığı:0.93-1.66, p<0.001) zirve TnT seviyelerinin bağımsız prediktörleri olarak tanımladı.
Sonuç: SII zirve TnT seviyelerinin bağımsız bir öngörücüsüdür ve AKS hastalarında zirve CK-MB seviyeleriyle anlamlı seviyede korelasyon göstermektedir. Ayrıca, SII sol ventrikül sistolik fonksiyonlarıyla anlamlı seviyede ters korelasyon göstermektedir.

Anahtar Kelimeler: Akut koroner sendrom, inflamasyon, sistemik immün-inflamasyon indeksi, troponin.

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INTRODUCTION

Acute coronary syndromes (ACSs) are classified according to various clinical circumstances related to acute myocardial ischemia or infarction and encompass ST-segment elevated myocardial infarction (STEMI), non-ST-segment elevated myocardial infarction (NSTEMI) and unstable angina pectoris (USAP). Cardiac troponins, including troponin I (TnI) and troponin T (TnT), are the main regulatory proteins within the myocardium that are secreted into the circulation subsequent to myocardial damage. Thus, they constitute the cornerstone biomarkers for the laboratory diagnosis of ACS [1, 2]. Besides, elevations in troponin levels exhibit prognostic features, including mortality, adverse cardiovascular outcomes and infarct size, in patients with ACS [3-6].

The pathogenesis of ACS, which results in atherosclerotic plaque rupture and subsequent thrombosis, is multifactorial and involves complex and various cascades of local and systemic alterations of inflammation and immune system activity. Neutrophils, platelets and lymphocytes are the principal cellular components of this process [7]. Systemic immune inflammation index (SII), which brings together the counts of these cells, is a novel marker that represents the balance between inflammation and the immune system. The predictive capability and prognostication of SII have been proven in various cardiovascular situations, including coronary artery disease (CAD), aortic stenosis and contrast-induced nephropathy after percutaneous coronary intervention (PCI) [8-11]. However, to our knowledge, there are no data in the literature investigating the relationship between SII and biomarkers of myocardial damage, such as troponin in ACS. Accordingly, the present study sought to investigate whether SII was associated with peak TnT measurements in patients with ACS.

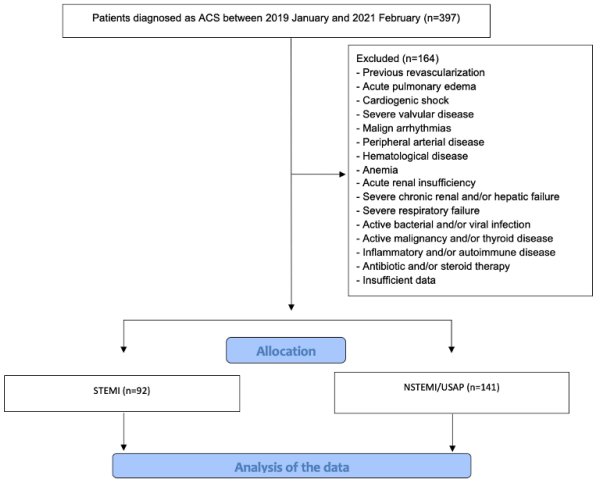
METHODS

Study Protocol and Participants

This study was designed in a retrospective and observational fashion and included 397 patients with ACS between January 2019 and February 2021. Consecutive ACS patients hospitalized in the cardiology department and underwent coronary angiography (CAG) participated in this study. Basal demographics and clinical characteristics, including medications, laboratory parameters and CAG data, were provided using an electronic database. The study protocol was approved by the local ethics committee (2017-KAEK-189_2021.02.10_11), and all study procedures were conducted in line with the Helsinki Declaration. Informed consent was waived due to the retrospective design of this study.

Previous coronary revascularization procedures, including PCI and coronary artery bypass graft (CABG), acute pulmonary edema, cardiogenic shock, severe valvular disease, presence of malign arrhythmias, peripheral arterial disease, active hematological disease, anemia, acute renal insufficiency, severe chronic renal and/or hepatic failure, severe respiratory failure, active bacterial and/or viral infection, active malignancy and/or thyroid disease, inflammatory and/or autoimmune disease, antibiotic and/or steroid therapy, were determined as exclusion criteria. Moreover, patients with insufficient data were excluded from this study. After the exclusion of 164 patients with the above criteria, 233 patients were allocated into STEMI (n=92) and NSTEMI/USAP (n=141) groups and included in statistical analyses (Figure 1).

Figure 1. Flow-chart diagram of the study.



ACS, acute coronary syndrome; NSTEMI, Non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; USAP, unstable angina pectoris.

Definitions

The diagnosis of ACS was performed according to current guidelines using anamnesis, electrocardiography (ECG), imaging methods and troponin levels. Patients with new-onset symptoms suggestive of ischemia, such as chest discomfort or pain and persistent ST-segment elevation on ECG, were diagnosed as STEMI [12]. Patients with new-onset symptoms suggestive of ischemia, no persistent ST-segment elevation on ECG and accompanying cardiac troponin increase greater than the upper limit of normal level were diagnosed as NSTEMI, whereas patients with new-onset symptoms suggestive of ischemia, no persistent ST-segment elevation on ECG without cardiac troponin increase were diagnosed as USAP [13]. Previous diagnosis of arterial hypertension (HT) with or without drug usage or mean office blood pressure measurements ≥140/90 mmHg at multiple measurements was described as arterial HT. Diabetes mellitus (DM) was described as fasting plasma glucose level ≥126 mg/dL in multiple tests or glucose level ≥200 mg/dL at any test or usage of antidiabetic therapies. Smoking was described as current smoking in the last six months. Hyperlipidemia was diagnosed as basal cholesterol measurement above 200 mg/dl and/or low-density lipoprotein (LDL) cholesterol measurement above 130 mg/dl or usage of hypolipidemic agents.

Laboratory Measurements

Peripheral venous blood sampling was performed from a large antecubital vein at the time of hospital admission, and measurements were made immediately. Total complete blood count test was administered using an automated blood cell counter (Sysmex XN-1000, Kobe, Japan) and admission SII levels were calculated as platelet count x neutrophil count/lymphocyte count [8]. Blood chemistry parameters, including cholesterol panel, were evaluated using standard methods.

C-reactive protein (CRP) levels were determined using the turbidimetric method (Roche Cobas 6000 c501) (normal reference values 0.15-5 mg/L) at admission. Serum levels of cardiac enzymes, including high-sensitivity TnT (Roche Cobas 6000 e601) (99th percentile 14 ng/L) and creatine kinase-myocardial band (CK-MB) (Roche Cobas 6000 c501) (99th percentile 6.73 ng/mL for men and 3.77 ng/mL for women), were measured using an electrochemiluminescence immunoassay method at the time of admission and repeated daily during patients' hospital stay. Reference values were calculated with a coefficient of variation <10% [14, 15].

Procedures and Medications

According to the physician's preferred access site, CAG was carried out through the standard Judkins technique (Allura Xper FD10, Philips Healthcare, the Netherlands) using femoral or radial route. Conventional coronary angiography images were recorded in multiple projections for all coronary arteries and PCI procedures were carried out immediately after diagnostic CAG when appropriate. During CAG and PCI procedures, the operator was free to decide revascularization type and technique, such as bare metal or drug-eluting stent implantation and bifurcation or provisional technique, choice of antithrombotic and anticoagulant therapy, and glycoprotein IIb/IIIa receptor antagonist administration. During their hospitalization times, all patients were followed up and treated in line with the recommendations of the international guidelines.

Two-dimensional transthoracic echocardiography (Philips Logic Affiniti 50G, Philips, Amsterdam, the Netherlands) was performed on patients at the left lateral decubitus position during their hospital stay. Left ventricular ejection fraction (LVEF) was calculated using Simpson's method. All echocardiographic procedures were in line with the recommendations of the American Society of Echocardiography [16].

Statistical Analysis

All statistical tests were exerted using IBM SPSS Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, New York, USA). The distribution pattern of numerical variables was tested by the One-sample Kolmogorov-Smirnov test. Afterwards, independent two samples t-test was applied to normally distributed numerical data, and the results were given as mean and standard deviation. The Mann-Whitney U test was applied for the abnormally distributed numerical data, and results were given as median with interquartile range

(percentiles 25th and 75th). Categorical variables were tested using Chi-square test or Fisher Exact test. Logarithmic transformations were applied to abnormally distributed data to yield an approximately normal distribution. The correlation of SII with various parameters was tested by Spearman's correlation analysis. Afterwards, the correlation between log-SII and log-peak TnT was tested using Pearson's correlation analysis.

Variables associated with peak TnT levels were investigated using univariate and multivariate linear regression analyses and the results were given with beta coefficient and 95% confidence interval (CI). Variables, which could be related to peak TnT levels, such as age, gender, DM, HT, LDL, log-creatinine, log-CRP and log-SII, were included in univariate analyses. The variables that reached a p-value below 0.1 in univariate tests were included in the multivariate model. A two-sided p-value below 0.05 was determined as statistically significant for all tests.

RESULTS

There remained 233 patients with ACS with 61±11 years old and percentage of male gender 74% after exclusion criteria were applied. Afterwards, patients were classified as STEMI (n=92) and NSTEMI/USAP (n=141). Baseline demographics and previous medications were comparable between the groups except for HT, hyperlipidemia and antiplatelet therapy. The number of diseased vessels was similar, whereas LVEF was significantly decreased in STEMI patients compared to NSTEMI/USAP patients (p<0.001). Culprit coronary artery and treatment of choice, including medical therapy, CABG and PCI, also significantly differed among groups (p<0.001 for both) (Table 1).

Regarding the laboratory parameters, there was no difference between groups regarding glucose, hemoglobin, blood urea nitrogen, creatinine, gamma-glutamyl transferase and total bilirubin levels, whereas aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase (LDH) levels were higher in STEMI patients at a significant level. On the contrary, total cholesterol and triglyceride measurements were significantly increased in NSTEMI/USAP group. Admission CRP levels were comparable among the two groups. Peak CK-MB and TnT levels were significantly higher in the STEMI group (p<0.001 for both). Besides, white blood cell and neutrophil counts were significantly elevated, and lymphocyte count was significantly decreased in STEMI patients. There was no difference among groups concerning platelet and monocyte counts. The median of SII levels was higher in STEMI group patients compared to NSTEMI/USAP group (1241, 646, p<0.001, respectively) (Table 2).

Table 1. Baseline demographic and clinical characteristics of the study population

Variables	All (n= 233)	STEMI (n=92)	NSTEMI/ USAP (n=141)	P value
Age	61±11	61±10	61±11	.955
Gender, male	173 (74%)	67 (73%)	106 (75%)	.688
Body mass index, kg/m2	29±5	30±5	29±5	.832
Smoking	86 (42%)	39 (48%)	47 (38%)	.160
Diabetes mellitus	96 (41%)	37 (40%)	59 (42%)	.805
Hypertension	111 (48%)	34 (37%)	77 (55%)	.008
Hyperlipidemia	139 (61%)	48 (53%)	91 (%67)	.032
Previous medications				
Beta-blocker	33 (14%)	10 (11%)	23 (16%)	.244
Calcium channel blocker	34 (15%)	16 (17%)	18 (13%)	.328
RAAS blocker	62 (27%)	22 (24%)	40 (29%)	.433
Antiplatelet	43 (19%)	9 (10%)	34 (24%)	.006
Statins	26 (11%)	8 (9%)	18 (13%)	.355
Oral antidiabetic	64 (27%)	21 (23%)	43 (31%)	.200
Insulin	21 (9%)	9 (10%)	12 (9%)	.740
Number of diseased vessels	1.6±0.9	1.7±0.7	1.6±1.0	.471
Left ventricle ejection fraction, % *	52±10	44±6	54±9	<.001
Culprit coronary artery				<.001
Left anterior descending artery	111 (54%)	42 (46%)	69 (62%)	
Circumflex artery	35 (17%)	10 (11%)	25 (22%)	
Right coronary artery	56 (27%)	40 (44%)	16 (14%)	
Intermediate artery	1 (1%)	0	1 (1%)	
Left main coronary artery	1 (1%)	0	1 (1%)	
Treatment procedure				<.001
Medical therapy	39 (17%)	1 (1%)	38 (27%)	
Coronary artery bypass grafting	27 (12%)	0	27 (19%)	
Percutaneous coronary intervention	166 (72%)	91 (99%)	(54%)	

NSTEMI, Non-ST-segment elevation myocardial infarction; RAAS, renin-angiotensin-aldosterone system; STEMI, ST-segment elevation myocardial infarction; USAP, unstable angina pectoris.* Left ventricular ejection fraction data was present in 98 patients.

Correlation analysis of SII with various clinical and laboratory parameters demonstrated a significant correlation with CRP (r=0.15, p=0.03), peak CK-MB (r=0.52, p<0.001), peak TnT (r=0.49, p<0.001), LDH, high-density lipoprotein, LVEF (r= -0.48, p<0.001) and number of diseased vessels (Table 3). Correlation analysis between log-SII and log-peak TnT levels also yielded a positive and significant correlation (r=0.44, p<0.001) (Figure 2).

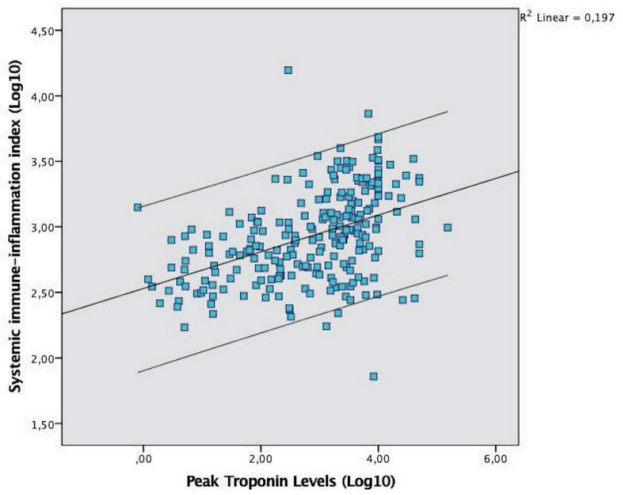


Figure 2. Correlation between the log-systemic immune-inflammation index and log-peak troponin T levels.

Linear regression analyses, including univariate and multivariate tests, showed that age, LDL, log-CRP and log-SII were associated with peak TnT in univariate analyses. In multivariate analyses, age and log-SII (Beta Coefficient: 1.29, 95 CI%:0.93-1.66, p<0.001) remained as independent predictors of peak TnT levels (Table 4).

DISCUSSION

Our results emphasize that SII is independently associated with peak TnT levels and significantly correlates with diverse markers of myocardial injury, such as peak CK-MB in ACS patients. Moreover, SII significantly and inversely correlates with left ventricular systolic functions. To our knowledge, this is the first study in the literature demonstrating an association between SII and markers of myocardial injury in an ACS patient population.

Atherosclerotic plaque formation with local and systemic activation of inflammation and immune system related cells are considered the main pathophysiological steps for ACS occurrence [7]. Neutrophils infiltrate into endothelial tissue, activate vascular inflammation and plaque erosion by secreting inflammatory mediators, which subsequently cause, atherothrombosis [17]. Lymphocytes reflect immune system activity and the number of lymphocytes decreases in ACS due to systemic stress [18]. Furthermore, lymphopenia is known to be linked with worse outcomes in CAD [19]. In general, leukocytosis, neutrophilia, and lymphopenia are thought of as a body response to systemic stress and related to worse prognosis, specifically in situations where inflammatory activity plays a major role, such as ACS [18]. On the other hand, platelets participate in all stages of inflammation and the atherothrombotic process by mediating leukocyte and progenitor cell recruitment into vascular injury sites and by secreting chemokines and cytokines that mediate vascular inflammation [20].

The pathophysiological contribution of these cell types in ACS and alterations in their counts have led the researchers to develop new biomarkers that reflect the inflammatory activity. These biomarkers are primarily derived from hematological parameters, such as neutrophil, platelet and/or lymphocyte cell counts. For example, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are well-defined inflammation-related biomarkers which are easily derived from a complete blood count examination and their associations with adverse cardiovascular outcomes were already demonstrated [21-23]. On the other hand, SII includes neutrophils, platelets and lymphocytes and identifies the balance of inflammation and immune system. The prognostic advantage of SII on NLR and PLR has been well-documented in cancer patients [24, 25]. Furthermore, the findings in a current study suggest that SII can predict functionally significant CAD better than NLR and PLR [9]. Accordingly, we hypothesized that SII is associated with peak TnT levels as a reflection of the extent of myocardial injury in ACS. Our findings have demonstrated that SII is an independent predictor of peak TnT levels and significantly correlates with peak CK-MB levels. Moreover, SII significantly and inversely has correlated with left ventricular systolic functions. In our analyses, SII as an inflammation-related

marker has also correlated with CRP levels.

Table 2. Laboratory findings of the study population

Variables	All (n= 233)	STEMI (n=92)	NSTEMI/ USAP (n=141)	p value
Glucose, mg/dL	158±85	167±84	152±86	.191
Hemoglobin, g/dL	14.2±1.8	14.2±1.8	14.2±1.7	.908
Blood urea nitrogen, mg/dL	16±6	16±6	16±5	.488
Creatinine, mg/dL	0.80 (0.70-0.93)	0.80 (0.70-0.90)	0.80 (0.70-0.96)	.580
Aspartate aminotransferase, U/L	29 (18-65)	63 (29-108)	22 (16-33)	<.001
Alanine aminotransferase, U/L	26±18	30±22	24±14	.014
Gamma-glutamyl transferase, U/L	22 (16-31)	21 (15-28)	22 (16-34)	.273
Lactate dehydrogenase, U/L	293±193	381±257	234±97	<.001
Total bilirubin, mg/dL	0.4 (0.3-0.6)	0.5 (0.3-0.6)	0.4 (0.3-0.6)	.597
Total cholesterol, mg/dL	191±42	183±39	195±43	.029
Low-density lipoprotein, mg/dL	119±37	119±36	119±38	.988
High-density lipoprotein, mg/dL	40±9	40±10	40±9	.923
Triglyceride, mg/dL	123 (83-210)	95 (70-144)	167 (100-237)	<.001
C-reactive protein, mg/L	4.0 (2.0-9.6)	4.3 (2.0-11.1)	4.0 (2.0-9.3)	.525
Peak creatine kinase-MB, ng/mL	35 (8-99)	102 (52-221)	13 (4-39)	<.001
Peak troponin T, ng/L	1566 (127-4592)	4645 (2802-9674)	283 (32-1548)	<.001
White blood cells, x 103	10.2±3.1	11.6±3.4	9.2±2.5	<.001
Neutrophils, x 103	7.2±2.9	8.8±3.0	6.2±2.4	<.001
Lymphocytes, x 103	1.9 (1.3-2.7)	1.6 (1.1-2.4)	2.0 (1.5-2.7)	.001
Platelets, x 103	243±59	244±66	242±55	.871
Monocytes, x103	0.6±0.3	0.7±0.3	0.6±0.2	.246
Systemic immune-inflammation index, x103	834 (467-1506)	1241 (665-2234)	646 (397-1080)	<.001

MB, myocardial band; NSTEMI, Non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; USAP, unstable angina pectoris.

Cardiac troponins are widely utilized for the diagnosis of ACS. In addition to being an ideal diagnostic marker, troponin measurements also provide prognostic benefits, such as estimation of infarct size after ACS. For example, a recent cardiac magnetic resonance imaging study showed that high-sensitivity TnT accurately predicts systolic function impairment in patients six months after first STEMI [14]. Similarly, TnI measurement at 72 hours after primary PCI strongly correlated with infarct size at five and 30 days and independently predicted adverse clinical events in STEMI patients [26]. At this point, it is reasonable to question the contribution of inflammation to myocardial damage in ACS. Evidence coming from a previous study indicates that an increase in troponin levels is independently associated with elevated CRP levels in NSTEMI [15]. Admission white blood cell and neutrophil counts were strongly related to infarct size in anterior STEMI [27]. Furthermore, NLR was linked with myocardial damage assessed using CK-MB measurements and systolic dysfunction detected through echocardiographic calculations in patients with ACS [28]. In another study, NLR negatively correlated with LVEF measurements and independently predicted systolic dysfunction in NSTEMI patients [29]. Consistent with these findings, we found that SII, which is an inflammation and immune system related marker, independently predicted peak TnT levels and inversely correlated with LVEF in patients with ACS.

Table 3. Correlation analysis of systemic immune-inflammation index with various parameters

	Systemic immune-inflammation index	
	r coefficient	p-value
Age	0.10	.109
C-reactive protein	0.15	.038
Peak creatine kinase-MB	0.52	<.001
Peak troponin T	0.49	<.001
Lactate dehydrogenase	0.54	<.001
Low-density lipoprotein	0.06	.387
High-density lipoprotein	0.14	.034
Left ventricle ejection fraction *	-0.48	<.001
Number of diseased vessels	0.22	.001

r coefficient= Spearman's rho, MB, myocardial band. * Left ventricular ejection fraction data was present in 98 patients.

Table 4. Univariate and multivariate linear regression analysis for variables associated with peak troponin levels

Variables	Peak Troponin Levels			
	Univariate		Multivariate	
	Beta Coefficient (95% CI Lower/ Upper)	p-value	Beta Coefficient (95% CI, Lower/ Upper)	p-value
Age	0.02 (0.01/0.03)	.003	0.01 (0.01/0.03)	.018
Gender	-0.09 (-0.42/0.24)	.607	..	..
Diabetes mellitus	-0.10 (-0.39/0.19)	.497	..	..
Hypertension	-0.12 (-0.41/0.16)	.394	..	..
Creatinine (Log10)	-0.89 (-2.3/0.5)	.208	..	..
Low-density lipoprotein	0.01 (-0.01/0.01)	.028	0.01 (-0.03/0.01)	.944
C-reactive protein (Log10)	0.30 (0.03/0.57)	.030	0.12 (-0.12/0.36)	.338
SII (Log10)	1.41 (1.04/1.78)	<.001	1.29 (0.93/1.66)	<.001

Multivariate Model's Adjusted R2= 0.234, p-value <.001, CI, confidence interval; SII, Systemic immune-inflammation index.

Although cardiac troponins are the surrogate markers of ACS diagnosis, it should be mentioned that they may not be specific to the etiology of ACS in every circumstance, and it is unclear whether troponins are secreted entirely from the infarcted myocardium or ischemic and/or failing cardiomyocytes also secrete troponin [14]. CK-MB is less cardiac-specific when compared to troponin, but previous data suggest that peak CK-MB is an independent predictor of LV functions and one-year mortality after primary PCI in patients with STEMI [30]. In our analysis, we found a significant correlation between SII and peak CK-MB levels. Considering as a whole, our results may provide pathophysiological insights into myocardial damage in ACS and contribute to biomarker investigations from a diverse perspective. Because both inflammation and the immune system play significant roles in the pathogenesis of ACS, SII, which is a marker that identifies the balance between the inflammation and immune system at a systemic level, may yield superior benefits when compared to other biomarkers and/or evaluation modalities. Moreover, it is a cheap and non-invasive test that is derived easily through a complete blood count examination. The utility of SII deserves to be investigated in various cardiovascular conditions.

Our study has several limitations that need to be underlined. A small number of patients, single-center design and retrospective nature of this study should be acknowledged. Although cardiac enzyme measurements were performed regularly, the lack of specified fixed time points and variations between blood sampling might have yielded a misrepresentation in true peak levels. Lack of echocardiographic data in some patients may be associated with selection bias which needs to be debated in well-designed future prospective studies. Besides, it is incomprehensible from the present data whether left ventricular systolic dysfunction is present before the ACS or it is a consequence of ACS. Furthermore, utilizing follow-up SII and CRP levels instead of only admission levels could provide more beneficial results. Thus, our observational and retrospective analysis should be considered hypothesis-generating only.

In conclusion, SII is independently associated with peak TnT levels and significantly correlates with peak CK-MB levels in ACS patients. Moreover, SII significantly and inversely correlates with left ventricular systolic functions.

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The evaluation of sperm DNA damage in patients with different varicocele grades

Farklı varikosel dereceli hastalarda sperm DNA hasarının değerlendirilmesi

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ABSTRACT

Aim: Varicocele, abnormal dilatation of pampiniform venous plexus, is classified into three groups: 1st, 2nd and 3rd grade. The aim of our research is to show the differences among the three different varicocele grades based on the results of their sperm DNA damage and blood biochemical parameters.
Methods: We examined 30 patients which were classified into three groups: Group 1 (healthy), Group 2 (grades 1 and 2) and Group 3 (grade 3). The semen samples were examined in terms of DNA damage via comet assay. The blood samples were assessed using catalase (CAT), superoxide dismutase (SOD) enzyme activities and malondialdehyde (MDA) levels.
Results: According to the comet findings, Group 2 and Group 3 parameters were significantly higher than Group 1 ($p < 0.01$). In the biochemical findings, we observed decreased CAT and SOD activities and an increased MDA level for Group 2 and Group 3. In our research, we showed that grades 1 and 2 had significant DNA damage in terms of infertility as much as grade 3.
Conclusion: The results we derived indicate that the detection of DNA damage could be used as a predictor of infertility alongside routine semen and morphological analysis.

Key words: Varicocele, infertility, spermatozoa, DNA damage.

ÖZ

Amaç: Pampiniform venöz pleksusun anormal dilatasyonu olan varikosel üç gruba ayrılır: 1., 2. ve 3. derece. Araştırmamızın amacı, sperm DNA hasarı sonuçlarına ve kan biyokimyasal parametrelerine göre üç farklı varikosel derecesi arasındaki farklılıkları göstermektir.
Method: Grup 1 (sağlıklı), grup 2 (1. ve 2. derece) ve 3. grup (3. derece) olmak üzere üç gruba ayrılan 30 hastayı inceledik. Semen örnekleri comet testi ile DNA hasarı açısından incelendi. Kan örnekleri katalaz (CAT), süperoksit dismutaz (SOD) enzim aktiviteleri ve malondialdehit (MDA) seviyeleri kullanılarak değerlendirildi.
Bulgular: Comet bulgularına göre grup 2 ve grup 3 parametreleri grup 1'e göre anlamlı derecede yüksekti ($p < 0.01$). Biyokimyasal bulgularda CAT ve SOD aktivitelerinin azaldığını ve grup 2 ve grup 3 için MDA düzeyinin arttığını gözlemledik. Araştırmamızda 1. ve 2. derece varikoselin infertilite açısından 3. derece kadar önemli DNA hasarına sahip olduğunu gösterdik.
Sonuç: Elde ettiğimiz sonuçlar, DNA hasarının saptanmasının, rutin semen ve morfolojik analizin yanı sıra infertilitenin bir prediktörü olarak kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Varikosel, İnfertilite, spermatozoa, DNA hasarı

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INTRODUCTION

Infertility has been defined as non-conception after one year in 20-25% of couples despite regular unprotected sexual intercourse in the absence of known reproductive pathology [1]. This rate decreases to 10–15% by the end of second year. Infertility is an important concern that can affect the psychological health and social life of couples. Male factor infertility has been regarded as a contributing factor causing infertility in 45-50% percent of cases, and as the sole cause for infertility in 15-20% percent of cases [1,2]. With regard to male infertility, it is believed to be the cause of up to 35% of primary infertility and 69-81% of secondary infertility [3]. In other studies in the literature, it is understood that varicocele is one of the most frequent reasons for male infertility, excluding the idiopathic ones [4].

The effect of varicocele on spermatogenesis in sub-fertile males is related to the low amount of sperm, decrease in sperm activity and abnormal sperm morphology [4,5]. The influence of varicocele on semen parameters and infertility is explained by many pathophysiologic mechanisms: testicular temperature increase, high venous pressure, hormonal dysfunctions, autoimmunity, epididymal dysfunction, acrosome reaction disorders, renal-adrenal reflux, DNA damage and oxidative stress [5]. DNA damage is one of the most researched mechanisms in the relationship between spermatogenesis and varicocele. Many studies have confirmed a high rate of sperm DNA damage in infertile males with varicocele [6,7]. Varicocele typically damages DNA through two mechanisms. First, varicocele increases DNA fragmentation by triggering mitochondrial inactivation. This increases sperm cell apoptosis by decreasing the level of soluble FAS gene that regulates the apoptosis [8,9]. The second one is oxidative stress which is the most studied mechanism. Varicocele causes a decline in DNA polymerase activity, which repairs DNA damage. High free oxygen radical levels can lead to more chromosomal breakages, an increase in DNA fragmentation and, therefore, disorders in acrosome unity towards infertility [10-13].

While researching varicocele cases, it is critical to perform semen analyses together with physical examinations after taking the medical and reproductive background history of patients. With respect to physical examination findings, varicocele can be classified into three groups: grade 1, grade 2 and grade 3 [14]. Varicocele is the most common cause of infertility, and it can be treated through surgery that usually recommended for grade 3 patients. Operation decision is a situation that varies according to the patient. Supportive therapies can be recommended in the patient group who have been diagnosed with varicocele but have no infertility problem or whose impairment in sperm parameters is limited [15].

The purpose of our study is to investigate sperm DNA damage by utilizing the comet assay in spermatozoa samples and to calculate the oxidative stress levels by determining MDA levels and SOD and CAT activities with blood samples in different varicocele grades. Actually, we aimed to show that varicocele grade 1 and 2 had significant DNA damage in terms of infertility as much as varicocele grade 3.

MATERIALS AND METHODS

Ethic Statement and Patients

This study included the sperm samples of 10 healthy males (control group) and 20 patients who applied to Erciyes University's Faculty of Medicine, Department of Urology, with complaints of inguinal pain, infertility and distension in the testicles, and who were therefore diagnosed with varicocele. The study sample was separated into three groups. Group 1 were determined to be healthy males (n=10), group 2 were varicocele grades 1 and 2 (n=10), and group 3 were varicocele grade 3 (n=10). Semen samples were taken from patients following a 3-day sexual abstinence. We used sterile and wide-mouthed plastic containers. Samples were stored in an incubator at 37°C to be liquefied. In addition, the blood samples taken from the same patients for biochemical analyses were stored at -80°C. Also, all procedure and protocols were approved by clinical research ethics committee at the University of Erciyes (number:2013/196).

Determination of Sperm DNA Damage Using The Comet Assay

Diluted sperm samples obtained from patients were centrifuged at 300 g for 10 min at 4 °C. The supernatant was removed and the remaining sperm cells were washed with phosphate buffered saline (PBS). Damaged sperms were determined using single cell gel electrophoresis (SCGE) method called comet assay under high alkaline conditions. The images of one hundred randomly chosen cell images from the sperm sample of each patient were visually analyzed and sperm with fragmented DNA were counted. All images were recorded by using a fluorescent microscope (Olympus, BX51, Japan) through 100X zoom. The damage was determined by calculating migrated heads and broken DNA tail forming a comet. The cell with the tail was defined as damaged and the one without the tail as undamaged.

Enzyme Activities Assay: Blood samples derived from all cases in EDTA tubes were centrifuged and kept at -80°C for biochemical analyses. All analyses were done in Erciyes University, Faculty of Medicine, Department of Biochemistry.

Malondialdehyde (MDA) Assay: Standards were prepared as stated in CAYMAN Tbars Assay kit protocol. Plasmas of blood samples were taken into glass tubes. In addition, 8 glass tubes were prepared for standards. Each tube was vortex plated by adding thiobarbituric acid-sodium dodecyl sulphate (TBA-SDS) solution after filling in 100 µl of either sample or a standard. After adding 4 ml of colour reactive, tubes were left in boiling water for 1 hour. Following this period, tubes were incubated in ice for 10 min to stop the reaction. By the end of incubation the tubes were centrifuged for 10 min at 1600 G at +4°C and add 150 µl to each well of the 96-plate. Absorbance tests at 540 nm wavelength were performed and recorded.

Superoxide Dismutase (SOD) Activity Assay: Standards were prepared in accordance with protocols given with CAYMAN Superoxide Dismutase kit. Each well was filled with 10 µl of sample or standard, 200 µl diluted radical detector and, finally, 20 µl diluted Xanthine Oxydase (KO), and the reaction was started to be incubated for 20 minutes in the shaker at room temperature. Absorbance tests at 460 nm wavelength were performed with plate reader and recorded.

Catalase (CAT) Activity Assay: Standards were prepared in accordance with protocols given with CAYMAN Catalase kit. Each well was filled with 20 µl sample, 30 µl methanol and 100 µl diluted assay buffer. The reaction was started with the addition of hydrogen peroxide (H2O2) to all wells. Wells were incubated for 20 minutes in the shaker at room temperature. In order to stop the reaction, 30 µl potassium hydroxide (KOH) was added and left for 10 minutes for incubation at room temperature following the addition of 30 µl catalase purpald into each well. Then, 10 µl catalase potassium periodate was added for incubation in shaker for 5 minutes at room temperature. Absorbance tests at 540 nm wavelength were performed with plate reader and recorded.

Statistical Analyses: The Shapiro-Wilks test was used to identify normal distribution of the data. Significant difference between two treatment groups was performed using one-way analysis of variance (ANOVA) followed by the post-hoc Tukey Test. P values less than 0.05 level were accepted as statistically significant.

RESULTS

Comet Assay Technique

In the current study, the alkaline comet technique was used to determine the single and double helix denaturations in sperm cell DNA of varicocele cases. Head length (length head), tail length (length tail), comet length (length comet), head % DNA (head DNA) and tail % DNA (tail DNA) parameters were analysed using Comet Assay Software Project-1.2.2 (CASP). The damage was determined through the calculation of migrated and comet-caused DNA tails. The extent of damage was calculated by adding parameters of tail length, fluorescence level at head and tail, and tail moment. The DNA fluorescence percentage of the tail is considered to be directly proportional to the frequency of DNA chain breakage. Comet assay results of groups are shown in Figure 1.

Head Length

It was statistically shown that the measured head lengths in Group 3 decreased compared to Group 1 and Group 2 ($p < 0.05$), however, no significant difference was observed between Group 1 and

Group 2 (p > 0.05). Results were shown in Figure 2.

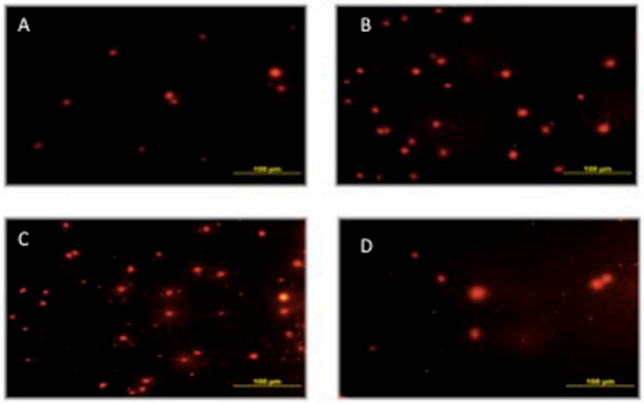

Figure 1. Intergroup sperm comet images A) Group 1 (Control Group), B) Varicocele Grade 1 1, C) Varicocele Grade 2, D) Varicocele Grade 3 (Ethidium Bromide Staining,x100)

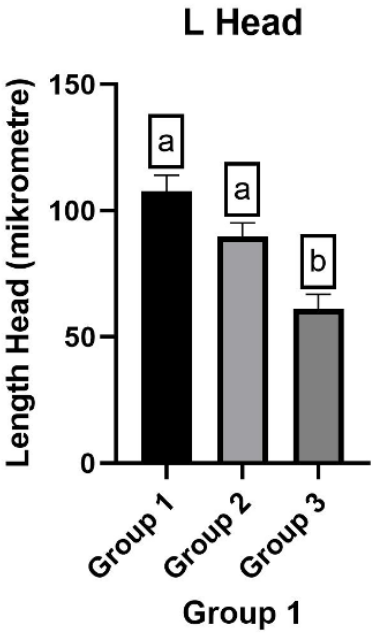

Figure 2. Statistical comparison of head length. There was a statistically significant difference between group 3 and the other groups (p < 0.05). However, no significant difference was founded between Group 1 and Group 2 (p > 0.05). While a statistical difference was observed between the groups labeled with different letters (p <005), there was no significant difference between the groups labeled with the same letter (p> 0.05).

Tail Length

The tail length measured in Group 2 and Group 3 showed a statistically significant increased compared to Group 1 (p < 0.05). Nevertheless, the difference between Group 3 and Group 2 was also statistically significant (p < 0.05). Results were shown in Figure 3.

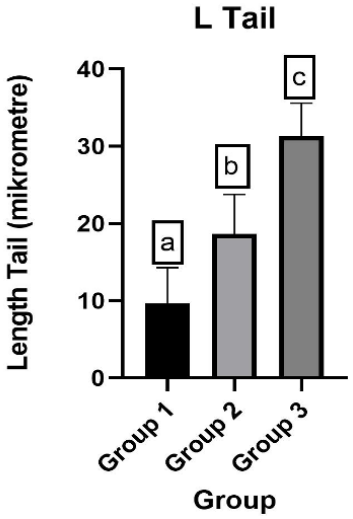

Figure 3. Statistical comparison of tail length. The tail length of Group 2 and Group 3 increased compared to Group 1 and this increased was found to be statistically significant. (p < 0.05). The most prominent increase was in Group 3 (p < 0.001). Statistical significant difference in groups was showed with different letters (p < 005).

Comet Length

A statistically significant increased was observed between Group 3 and the other groups (p < 0.05). However, no significant difference was observed between Group 1 and Group 2 (p > 0.05). Results were shown in Figure 4.

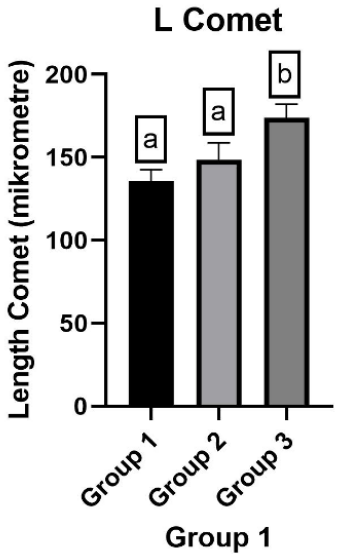

Figure 4. Statistical comparison of comet length. No significant difference was observed in comet length of Group 2 compared to Group 1 (p > 0.05). However, There was a statistically significant increased between group 3 and the other groups (p < 005). While a statistical difference was observed between the groups labeled with different letters (p <005), there was no significant difference between the groups labeled with the same letter (p> 0.05).

Percent Tail DNA

Percentage tail DNA measured in Group 3 and Group 2 increased gradually compared to Group 1 ($p < 0.05$). Looking at the findings, we can state that increase in percentage of tail DNA and varicocele grades are positively correlated to each other. Results were shown in Figure 5.

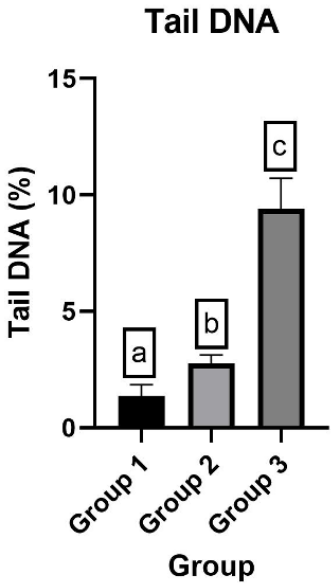

Figure 5. Statistical comparison of the percent tail DNA. Percentage tail DNA measured in Group 3 and Group 2 increased gradually compared to Group 1 ($p < 0.05$). Statistical significant difference in groups was showed with different letters ($p < 005$).

Percent Head DNA

Percentage DNA in the comet head measured in Group 2 and Group 3 decreased gradually compared to Group 1 ($p < 0.05$). There was a prominent decrease in the percent head DNA as the degree of varicocele increased among the groups ($p < 0.05$). According to the findings we can inform that decrease in percentage of head DNA and varicocele grades are positively correlated to each other. Results were shown in Figure 6.

Biochemical Results

Blood malondialdehyde (MDA) level, Catalase (CAT) and Superoxide Dismutase (SOD) enzyme activities were evaluated in blood samples by ELISA technique. CAT and SOD levels as indicators of oxidant/anti-oxidant presence and the MDA level as the indicator of lipid peroxidation were measured in the blood samples obtained from our cases. The measurement results are given in Table 1; $p < 0.010$ is accepted as statistically meaningful.

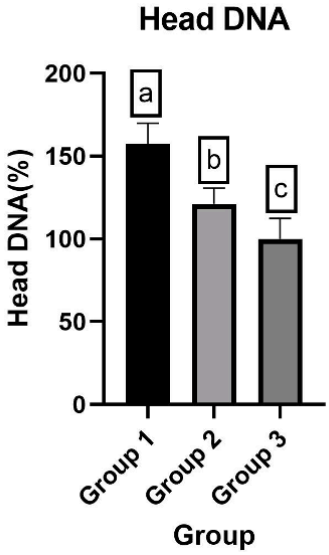

Figure 6. Statistical comparison of the percent head DNA. Percentage DNA in the comet head measured in Group 2 and Group 3 decreased gradually compared to Group 1 ($p < 0.05$). Statistical significant difference in groups was showed with different letters ($p < 005$).

Serum Malondialdehyde (MDA) Levels

MDA levels were measured in the serums of blood samples to determine the peroxidation level. MDA levels are given in Table 1. When intergroup MDA levels are compared, the MDA level of Group 3 was significantly higher than Groups 1 and 2 ($p < 0.010$). When the MDA level of Group 2 was compared to that of Group 1, it was higher, but lower than that of Group 3, and the result was statistically meaningful ($p < 0.010$).

Table 1. Statistical Comparison of Enzyme Parameters

	MDA (µM)	CAT (µM)	SOD (µM)
Group 1 (n=10)	17,64±9,67a	25,47±11,02a	0,23±0,19a
Group 2 (n=10)	75,01±32,22b	4,05±2,39b	0,06±0,09b
Group 3 (n=10)	118,96±52,10b	1,69±1,31b	0,02±0,05b
p	0,001	0,001	0,001

While a statistical difference was observed between the groups labeled with different letters ($p <005$), there was no significant difference between the groups labeled with the same letter ($p> 0.05$).

Serum Catalase (CAT) Activity

The mean CAT activities were measured in the serums of blood samples to determine the peroxidation in them and were given in Table 1. When Group 1 was compared to other groups, the

mean CAT activity was higher than that of other groups and this was statistically meaningful ($p < 0.010$). When Group 2 was compared to Groups 1 and Group 3, the activity level was lower than Group 1, and the result was statistically meaningful ($p < 0.010$); despite being higher than Group 3, it was not statistically meaningful ($p = 0.302$). However, when Group 3 was compared to Groups 1 and 2, we have observed that Group 3 was lower than Group 1 and this was statistically meaningful ($p < 0.010$) and lower than group 2 but not statistically meaningful ($p = 0.302$).

Serum Superoxide Dismutase (SOD) Activity

SOD activities were measured in the serums of blood samples to determine the peroxidation levels in them. SOD activities were given in Table 1. The mean SOD activity level of Group 1 was higher than that of the other groups, and this was statistically significant ($p < 0.010$). When Group 2 was compared to Groups 1 and Group 3, the mean SOD activity level was lower than Group 1, and the result was statistically meaningful ($p < 0.010$); despite being higher than Group 3, it was not statistically meaningful ($p = 0.530$). However, when Group 3 was compared to Groups 1 and 2, the result for Group 3 was lower than Group 1 and this was statistically prominent ($p < 0.010$). The result for Group 3 was lower than Group 2, but the result was not statistically remarkable ($p = 0.530$).

DISCUSSION

In the literature, there are many studies on varicocele and sperm DNA damage. The DNA quality in males is equivalent to reproductive ability. A DNA-damaged sperm can enable fertilization to proceed but is the subject of research due to the high possibility of aneuploidic embryos, early pregnancy losses, the risk of metabolic diseases as a result of epigenetic changes, and childhood cancers [17]. Recent studies have shown that varicocele has effects on semen parameters causing meaningful damage to sperm DNA, causing hormonal destruction by affecting the structure of Sertoli and Leydig cells in the testicles, and triggering direct oxidative damage by increasing Reactive Oxygen Species (ROS) levels [18]. In light of prior studies, in our study, we have investigated the sperm nuclear DNA damage and measured oxidative stress levels in patients with different grades of varicocele compared to normal healthy males. It is reported that sperm function may be damaged due to a dysfunctional acrosome or autoimmune reaction related to varicocele pathology [18]. Today, it is well-known that reactive oxygen radicals increasing secondarily to oxidative stress causes damage through lipid peroxidation in cells. The target of these reactive oxygen radicals is unsaturated fatty acids in the cell membrane, and they may affect any cell that has these acids. It is stated that as the sperm membrane is rich with unsaturated fatty acids, increasing reactive oxygen radicals due to varicocele pathology may also affect the sperm structure [11]. Köksal et al. [19] have demonstrated that reactive oxygen radicals with varicocele generated rats are higher in number than the normal population. In a study where left varicocele cases were examined, it has been reported that ROS was related to varicocele, and, therefore, there was an increase in DNA fragmentation [20]. Similarly, Allamaneni et al. [21] have reported that when varicocele grade 3 is compared to grades 1 and 2, seminal ROS levels were found to be meaningful. In another study conducted by Smith et al. [22] it has been stated after their research on the the mechanisms which play role in varicocele that males with varicocele had more free oxygen radical amounts in semen. In our study, we analysed ROS and antioxidant parameters in cases of different varicocele phases. Our results are in accordance with those of Allamaneni et al. [21], and we have shown that the varicocele grade was higher in parallel to higher ROS parameters, while antioxidant levels were meaningfully lower.

It is curious subject whether there is a relationship between DNA damage and parameters such as ROS in male infertility. Saleh et al. [23] have reported that damage to sperm DNA had a negative impact on fertility. The DNA damage caused by ROS accelerates cell apoptosis. This has a negative impact on reproduction biology due to low number of sperm. In many studies, it has been stated that the determination of sperm morphology was not sufficient to find the cause of infertility. Thus, many different techniques have been preferred for determining sperm DNA damage in recent past. However, some studies mention that such techniques used for the determination

of only sperm DNA damage have no superiority in morphologic evaluation [24]. We have analysed sperm DNA damage together with blood oxidative stress levels, and we have concluded that there was a positive correlation between the two. Ying-Jun Wang et al. [25] have shown in a meta-analysis of 83 independent studies on varicocele and sperm DNA damage published between 1963 and August 2011 that the best techniques for determining sperm DNA damage were terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), comet assay and sperm chromatin structure assay (SCSA). Simon et al. [26] have performed a spermatozoon analysis in three groups for DNA damage in infertile couples by using comet assay with the idea that sperm DNA damage affects embryo quality: low damage, medium damage and high damage. The reasons for the infertility of these couples were in three groups: male, female and undefined. Each embryo was categorized as good, medium or low quality; when they were compared in terms of the effect of sperm DNA damage on embryo quality, the spermatozoon group with low DNA damage was meaningfully higher with high quality embryo percentages. Therefore, we have utilized comet assay in order to show the DNA damage in different grades of varicocele in our study. comet assay is often preferred for DNA damage measurements as it is simple, fast, precise, applicable for different cell types and DNA damages, and, most importantly, it does not require any radioactive labelling [27].

Conclusion: The present study concluded that there was more sperm DNA damage in varicocele grades 1 and 2 cases than expected, and there was high DNA damage in all varicocele grade 3 cases. Our comet findings are concordant with biological parameters. This condition may imply that varicocele grade 1 and 2 are significant DNA damage in terms of infertility as much as varicocele grade 3. Therefore, the detection of DNA damage could be used as a predictor of infertility alongside routine semen and morphological analysis.

Conflict of Interest: No conflict of interest was declared by the authors.

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Ethics Committee Approval: Board name: Erciyes University clinical research ethics committee, Date anda number: 2013/196

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Evaluation of Anti-DFS70 antibodies and DFS pattern in ANA positive individuals and ANA Associated Rheumatic Diseases

ANA Pozitif Bireylerde ve ANA İlişkili Romatizmal Hastalıklarda Anti-DFS70 Antikorlarının ve DFS Paterninin Değerlendirilmesi

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ABSTRACT

Aim: In this study we aimed to find the frequency of anti-DFS70 antibodies and DFS pattern in ANA positive individuals and ANA associated rheumatic diseases (AARDs).
Methods: In this study, 337 subjects who were evaluated in a rheumatology clinic with prediagnosis of rheumatic diseases with positive ANA test and had concurrent anti-extractable nuclear antigen (anti-ENA) antibodies results were retrospectively analyzed. Clinical diagnosis of patients and demographic characteristics were obtained from the patients' medical records.
Results: A total of 337 subjects (305 women, 32 men) were included in this study. The mean age was 49.8 ± 14.2 years. Of the 337 participants, 111 (32.9%) had an IIF-DFS pattern and 226 (67.1%) had a non-DFS pattern. Anti-DFS70 antibodies were positive in 20.1% of individuals. Sixty eight individuals had AARDs. An IIF-DFS pattern was observed in 22.1% and a non-DFS pattern was observed in 77.9% of individuals with AARDs ($p < 0.05$). Anti-DFS70 antibodies were positive in 13.2% of patients with AARDs. The frequency of AARDs was significantly lower in individuals with anti-DFS70 antibodies compared to individuals with other anti-ENAs antibodies ($p < 0.05$).
Conclusion: Anti-DFS70 antibodies may be present in patients with AARDs but AARDs are less prevalent in patients who had anti-DFS70 antibodies, compared with patients who had other anti-ENAs.

Key words: Antinuclear antibodies (ANA), Anti DFS70 antibody, DFS pattern

ÖZ

Amaç: Bu çalışmada, ANA pozitif bireylerde ve ANA ilişkili romatizmal hastalıklarda anti-DFS70 antikor ve DFS patern sıklığını bulmayı amaçladık.
Yöntem: Bu çalışmada romatoloji kliniğinde romatizmal hastalık ön tanısı ile değerlendirilen, ANA tetkiki pozitif olan ve eş zamanlı anti-ekstrakte edilebilir nükleer antijen (anti-ENA) antikor sonucu olan 337 kişi retrospektif olarak incelendi. Hastaların klinik tanıları ve demografik özellikleri hasta tıbbi kayıtlarından elde edildi.
Bulgular: Bu çalışmaya toplam 337 (305 kadın, 32 erkek) kişi dahil edildi. Yaş ortalaması 49.8±14.2 yıl idi. 337 katılımcının 111'i (%32.9) IIF-DFS paterne, 226'sı (%67.1) DFS dışı paterne sahipti. Bireylerin %20.1'inde anti-DFS70 antikoru pozitifti. 68 kişide ANA ilişkili romatizmal hastalık vardı. ANA ilişkili romatizmal hastalığa sahip kişilerin %22.1'inde IIF-DFS patern, %77.9'unda DFS dışı patern gözlendi ($p<0.05$). ANA ilişkili hastalığa sahip kişilerin %13.2'sinde anti-DFS70 antikoru pozitifti. Anti-DFS70 antikoruna sahip kişilerde diğer anti-ENA antikorlarına sahip kişilerle karşılaştırıldığında ANA ilişkili romatizmal hastalık sıklığı anlamlı ölçüde düşüktü ($p<0,05$).
Sonuç: Anti-DFS70 antikorlar ANA ilişkili romatizmal hastalıklarda bulunabilir ancak ANA ilişkili romatizmal hastalıklar anti-DFS70 antikorlarına sahip kişilerde diğer anti-ENA antikorlarına sahip kişilere kıyasla daha az yaygındır.

Anahtar kelimeler: Anti nükleer antikorlar (ANA), Anti DFS70 antikor, DFS patern

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INTRODUCTION

Antinuclear antibodies (ANA) are assay markers for diagnosis of ANA associated rheumatic diseases (AARDs) such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SjS), mixed connective tissue disease (MCTD) and systemic sclerosis (SSc) [1]. The indirect immunofluorescence (IIF) assay is mostly used for the detection of ANA and proposed as a screening test by the American College Rheumatology (ACR) [2]. Anti-Dense Fine Speckled 70 (DFS70) antibodies were identified as related to specific IIF-ANA pattern. The DFS pattern is characterized by irregularly distributed, fine-granular fluorescence of the nuclei and has shown reactivity of the autoantibody with a 70 kD protein [3,4]. Anti-DFS70 antibodies are related with different status [5]. DFS70 pattern and anti-DFS70 antibodies have been stated more commonly in healthy individuals compared to systemic rheumatic diseases [6,7]. Anti-DFS70 antibodies have been defined as an eventual marker for the ruling out systemic autoimmune diseases (SARDs) [8].

In this retrospective study we aimed to determine the frequency of anti-DFS70 antibodies and IIF-DFS pattern in IIF-ANA positive individuals and patients with AARDs.

MATERIALS AND METHODS

In this retrospective study, 337 subjects with positive ANA test and who simultaneously had anti-ENAs antibodies results and who were evaluated with a prediagnosis of rheumatic diseases in the rheumatology outpatient clinic between 2018 and 2019, were consecutively included. ANA was detected using the indirect immunofluorescence (IIF) method (IIF Mosaic: Hep-20-10/Liver (Monkey) kit, Euroimmun, Germany). ANA at titer ≥ 1/160 was considered as positive. An ANA Profile 3 plus DFS70-IgG kit (Euroimmun, Germany) was used for the anti-ENAs test. Autoantibodies against nuclear ribonucleoprotein (nRNP), Smith (Sm), SS-A/Ro-52, SS-B, Scl-70, PM-Scl, Jo-1, centromere protein B (CENP-B), double-stranded DNA (dsDNA), nucleosome, histone, ribosomal P-protein and anti-mitochondrial antibodies (AMA) autoantigens were evaluated in the ANA profile. Demographic characteristics of the individuals, ANA pattern, anti-ENAs test results and diagnosis of AARDs were recorded from the electronic file. AARDs consisted of SLE, SS, undifferentiated connective tissue disease (UCTD), SSc, myositis, drug induced SLE and SLE/SSc overlap.

Statistics: Categorical data is shown as counts and percentages. Continuous data is shown as means and standard deviations (SD). The Pearson chi-square test was used to compare the qualitative results. The IBM-SPSS16 was used in all statistical analyses and the p value <0.05 was considered statistically significant. This study was performed according to the Declaration of Helsinki. Permission for the study was obtained from the Balıkesir University Faculty of Medicine Ethics Committee, decision number 190 in 04/12/2019.

RESULTS

In this study a total of 337 individuals (305 female, 32 male) with positive ANA and simultaneously anti-ENAs test results were included. The mean age was 49.87±14.29 years (female: 50.10±13.92 years, male: 47.75±17.49 years p>0.05). An IIF-DFS pattern was observed in 32.9% of 337 individuals.

Anti-DFS70 antibodies were positive in 68 (20.2%) of the 337 subjects (Table 1). Among these, 64 (94.1%) had isolated anti-DFS70 antibody (anti-DFS70 antibody positive, with other anti-ENAs being negative). Among anti-DFS70 antibody positive subjects, four had additional anti-ENAs specificity (1 anti-SS-A, 1 pm-scl, 1 anti-histone, 1 anti-SCL-70 antibody). Anti-DFS70 antibodies were present in 54 of the 111 (48.6%) subjects with IIF-DFS pattern (53 isolated anti DFS70 antibodies positive, 1 additional anti ENAs being positive). Fourteen of 226 (6.2%) subjects with other IIF-ANA patterns had anti-DFS70 antibodies. Among DFS pattern positive subjects, 58 individuals had >1/160 titer, 37 individuals had ≥1/320 titer, 14 individuals had ≥1/640 titer and 2 individuals had ≥1/1280 titer. Anti-DFS70 antibodies were positive in 85% of the subjects who had IIF-DFS titers ≥1/640 and 43.1% of the subjects who had >1/160 IIF DFS titer. The mean age was 46.93±14.17 in subjects who had anti-DFS70 antibodies and 50.62±14.25 in subjects who did not (p<0.05).

Sixty-eight of 337 (20.1%) individuals had AARDs

(19 SLE, 21 SS, 21 UCTD, 3 SSc, 1 myositis, 2 drug induced SLE, 1 SLE/SSc overlap). The DFS pattern was observed in 22.1% of (15/68) patients with AARDs. The frequency of AARDs was 13.2% (15/111) in individuals with DFS pattern and 23.5 % (53/226) in individuals with non DFS pattern ($p<0.05$). The anti-DFS70 antibodies were positive in 13.2% (n=9) of 68 patients with AARDs. The other anti-ENAs antibodies were positive in 42.6% (n=29) of 68 patients with AARDs. The frequency of AARDs was significantly lower in the individuals with anti DFS70 antibodies compared to those with other anti-ENAs specificity ($p<0.05$). Among 68 patients with AARDs, 6 patients had isolated anti-DFS70 antibody positivity and 3 patients had additional anti-ENAs specificity. Clinical diagnosis of anti-DFS70 positive subjects were 3 UCTD, 2 SLE and 4 SS. The distribution of AARDs, according to IIF-DFS and anti DFS70 antibody status, is shown in (Table 2).

Table 1. Frequency of IIF-DFS, anti-DFS70 antibody and AARD

	noun/percent	
	Total (337)	AARDs (68)
IIF-ANA		
-ANA positive	337	68
-DFS pattern positive	111 (32.9)	15 (22.1)
-Non DFS pattern	226 (67.1)	53 (77.9)
IB Anti ENA		
-Anti-DFS70 positive	68 (20.2)	9 (13.2)
-İsolated anti DFS70 positive	64 (18.9)	6 (8.8)
-Anti-DFS70 and additional ENAs positive	4 (1.2)	3 (4.4)
-İsolated anti ENAs positive	39 (11.6)	29 (42.2)
IIF-ANA and Anti ENA Combination		
-DFS pattern positive and anti DFS70 positive	54 (16.02)	7 (10.2)
-DFS pattern positive and isolated anti DFS70 positive	53 (15.72)	6 (8.8)
-DFS pattern positive and anti DFS70 additional anti ENAs positive	1 (0.29)	1 (1.4)
-DFS pattern positive and isolated anti ENAs positive	4 (1.18)	3 (4.4)
-DFS pattern negative and anti DFS 70 positive	13 (3.85)	3 (4.4)

The positive predictive value of IIF-DFS pattern to detect AARDs was 13.5% and the positive predictive value of anti-DFS70 antibodies to detect AARDs was 13.2% (Table 3).

Table 2. The frequency of anti-DFS70 antibody and IIF-DFS pattern in AARDs.

	IIF DFS70 pattern N (%)	Non IIF DFS pattern	Anti DFS70 antibody (+)	Anti DFS70 antibody (-)	Total (n)
Systemic Lupus Eritematozus (SLE)	6 (5.4%)	13 (5.8%)	2 (3%)	17 (6.3%)	19
Sjögren Syndrome (SS)	6 (5.4%)	15 (6.6%)	4 (6%)	17 (6.3%)	21
Undifferansiye konnective tissue disease	3 (2.7%)	18 (8%)	3 (4.5%)	18 (6.7%)	21
Systemic Sclerosis		3 (1.3%)		3 (1.1%)	3
Drug induced SLE		2 (0.9%)		2 (0.7%)	2
SLE/SS overlap		1 (0.4%)		1 (0.4%)	1
Myositis		1 (0.4%)		1 (0.4%)	1
Total	15	53	9	59	68

Table 3. The IIF-DFS pattern and anti DFS70 antibody in detection of AARDs

n=337	IIF DFS pattern positive	Anti DFS70 antibody positive
AARD negative (n=269)	96	59
AARD positive (n=68)	15	9
Total	111	68

Discussion: In this study, we aimed to investigate the frequency of IIF-DFS pattern and anti-DFS70 antibodies in ANA positive individuals and determine whether IIF-DFS pattern and anti-DFS70 antibodies were important to exclude the diagnosis of AARDs. The DFS pattern has been defined as the AC-2 pattern by an international ANA consensus algorithm. Although the intensely stained metaphase chromosome plate is an important feature of the AC-2 pattern, the entire speckled nuclear patterns with positive staining of the metaphase plate are not all AC-2. Mahler et al. developed the "pseudo-DFS" pattern description and stated that this pattern was responsible for most of the AC-2 patterns that did not show anti-DFS70 reactivity [9,10]. In our study we found IIF-DFS pattern in 32.9% (111) of the 337 individuals. Carter et al. reported a DFS pattern in 32.9% of 5339 ANA positive samples. and Dellevance et al. reported 37% DFS pattern among 13641 ANA

positive samples [5,7]. The presence of anti-DFS70 antibodies was reported from 60.2% to 91 % in subjects with IIF-DFS pattern [11,12]. In our study, anti-DFS70 antibodies were positive in 48.6% of subjects with IIF-DFS pattern and the percent of anti-DFS70 antibody positivity was lower at a low titer IIF-DFS pattern, compared to high titer IIF-DFS patterns. Similar to our study, Jeon et al. found that the anti-DFS70 antibody positivity was lower at low titer IIF- DFS pattern [13]. In our study, anti-DFS70 antibodies were not positive in all individuals who had an IIF-DFS pattern. We think that our results may be related to a pseudo DFS pattern and IIF-DFS positivity should be confirmed with the anti-DFS70 antibody test. Anti-DFS70 antibodies are rarely seen in systemic rheumatic diseases and it has been reported that they can be used to rule out SARDs [14]. Mahler et al. showed that anti-DFS70 antibodies were more common in healthy individuals (8.9%) than patients with SARDs (2.8%) [15]. Inversely in a recent study, Infantino et al. found no differences between AARDs and non-AARDs individuals though in their study, all of anti-DFS70 antibody positive AARDs patients had concomitant anti-ENAs specificity [1]. Muro et al. detected the anti-DFS70 antibodies in 4.4% of 500 subjects with different types of rheumatic diseases. They emphasized that patients with isolated anti-DFS70 antibodies were infrequently diagnosed with autoimmune rheumatic diseases [16].

On the other hand, Peker et al. found that the frequency of anti-DFS70 antibodies was statistically significantly higher in subjects with SARDs compared to donor serums [17]. Türkoglu et al. found that anti-DFS70 antibodies were positive in 91.7% of subjects with IIF-DFS pattern and they reported that all subjects had isolated positivity [18]. In our study, isolated positivity was found in 94.1% of anti-DFS70 antibody positive individuals and 13.2% of subjects with AARDs were positive for anti-DFS70 antibodies. Anti-DFS70 positivity was statistically significantly lower in individuals with AARDs.

Our report supports that anti-DFS70 antibodies may be present in patients with AARDs, but AARDs are less prevalent in patients who had anti-DFS70 antibodies. Our study differentiates itself from other studies related with anti-DFS70 antibodies because we examined the predictive value of DFS pattern and anti-DFS70 antibodies for the diagnosis of AARDs and we found that the positive predictive values of DFS pattern and anti-DFS70 antibodies were very low. This finding supports that the fact that anti-DFS70 antibody positivity is an important marker to exclude AARDs.

Limitations: This study was designed retrospectively. The study group consisted of individuals who were evaluated with a prediagnosis of rheumatic disease. Prospective monitoring of whether AARDs will develop in subjects with anti-DFS70 antibodies will contribute to the determination of the role of anti-DFS70 antibodies in rheumatic diseases.

Conclusion: Anti-DFS70 antibodies may be present in patients with AARDs, but AARDs are less prevalent in patients who had anti-DFS70 antibodies compared to patients who had other anti ENAs specificity.

Conflict of Interest: The author declares no conflict of interest related to this article.

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The Potential Role of Uterine Retroversion in Pelvic Pain Symptoms and Caesarean Delivery

Pelvik Ağrı Semptomlarında ve Sezaryen Doğumunda Uterin Retroversiyonunun Potansiyel Rolü

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ABSTRACT

Aim: Uterin Retroversion is a common status in the women population and assumed to be related with pelvic pain symptoms. The aim of this study is to investigate whether uterine retroversion is associated with pelvic pain symptoms and is a reason for cesarean delivery.
Methods: One hundred thirty-three premenopausal women admitted in a Tertiary Education and Research Hospital, Department of Gynecology unit for pregestational counseling were evaluated for pelvic pain symptoms with a self-administrated questionnaire. Uterine position was assessed by pelvic examination and transvaginal ultrasound. Sixty-one women had a retroverted uterus (group1), and seventy-two had an anteverted or intermediate uterus (group2). Dyspareunia, dysmenorrhea, weight, Body Mass Index (BMI), cyclic pain, ovulation pain, premenstrual pain and mode of delivery were compared between the Retroverted group and the Anteverted or intermediate group. After successful conception and pregnancy survey, mode of delivery was also compared.
Results: Dyspareunia, dysmenorrhea, weight, BMI, cyclic pain, ovulation pain, premenstrual pain, patients' sexual activities restrictment due to dyspareunia, patients medical treatment requirement for dysmenorrhea, and mode of delivery was statistically significant between two groups. (p<0.05). However, PMS (premenstrual syndrome), height, gravid and parity were similar. (p>0.05)
Conclusions: Uterine retroversion is associated with a higher prevalence of cesarean rate, pelvic pain and visual analogue scale for dyspareunia and dysmenorrhea in a population of unselected women.

Keywords: Cesarean, Dysmenorrhea, Dyspareunia, Uterine retroversio

ÖZ

Amaç: Uterus Retroversiyonu kadın popülasyonunda yaygın bir durumdur ve pelvik ağrı semptomları ile ilişkili olduğu varsayılmaktadır. Bu çalışmanın amacı, uterus retroversiyonunun pelvik ağrı semptomları ile ilişkili olup olmadığını ve sezaryen doğum nedeni olup olmadığını araştırmaktır.
Yöntemler: Üçüncü Basamak Eğitim ve Araştırma Hastanesi Kadın Hastalıkları Kliniği'ne pregestasyonel danışmanlık için başvuran 103 premenopozal kadın, kendi kendine uygulanan anket formu ile pelvik ağrı semptomları açısından değerlendirildi. Uterus pozisyonu pelvik muayene ve transvajinal ultrason ile değerlendirildi. Altmış bir kadında uterusu retroverted (grup 1) ve yetmiş ikisinde ise ileri dönük veya orta uterus (grup 2) vardı. Retroverted grup ile Anteverted veya intermediate grup arasında disparoni, dismenore, ağırlık, Vücut Kitle İndeksi (BMI), döngüsel ağrı, yumurtlama ağrısı, adet öncesi ağrı ve doğum şekli karşılaştırıldı. Başarılı bir gebelik ve gebelik araştırmasından sonra, doğum şekli de karşılaştırıldı.
Bulgular: Disparoni, dismenore, kilo, VKİ, döngüsel ağrı, yumurtlama ağrısı, premenstrüel ağrı, disparoni nedeniyle hastaların cinsel aktivitelerinin kısıtlanması, dismenore için hastaların medikal tedavi gereksinimi ve doğum şekli iki grup arasında istatistiksel olarak anlamlıydı. (p <0.05). Bununla birlikte, PMS (adet öncesi sendrom), boy, ağırlık ve parite benzerdi. (p> 0.05)
Sonuçlar: Uterin retroversiyonu, seçilmemiş kadınlardan oluşan bir popülasyonda daha yüksek sezaryen oranı prevalansı, pelvik ağrı ve disparoni ve dismenore için görsel analog skala ile ilişkilidir.

Anahtar Kelimeler: Sezaryen oranı, Dismenore, Disparoni, Uterin retroversiyon

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INTRODUCTION

Uterine retroversion affects approximately 20% of all women [1]. In uterine anteversion, the uterus is tilted forward at the cervix. In contrast, in a retroverted uterus, the uterus is tilted backward at the cervix [1]. Several recent studies reported that uterine retroversion was responsible for pelvic-related pain, including dyspareunia and dysmenorrhoea, with dyspareunia and dysmenorrhoea reported in 90% and 40%, respectively, of uterine retroversion cases [2–4]. Some studies reported that in women with a retroverted uterus, surgical correction of the uterine axis to a neutral position provided symptom relief [3, 5]. Pelvic pain associated with uterine retroversion led to increased use of analgesic drugs and a decrease in quality of life.

The aim of this study was to investigate whether uterine retroversion was associated with pelvic pain and increased caesarean delivery rates. Based on the findings of the present study, surgery to correct the position of the uterus and follow-up of pregnant women with uterine retroversion are recommended to prevent possible complications associated with a retroverted uterus.

METHODS

This single-centre study was conducted between June 2019 and October 2020. One hundred and thirty-three premenopausal women who visited the Department of Obstetrics and Gynaecology of a tertiary education and research hospital for pregestational counselling were included in the study. The study was approved by the local ethics committee of Alaaddin Keykubat University (Approval no.: 24-3, 09.10.2020). Signed informed consent was obtained from all the volunteers. The study protocols were designed in accordance with the principles of the Helsinki Declaration, and they adhered to local guidelines on good clinical practice.

The inclusion criteria included pelvic pain in the last 6 months, sexually active and a regular menstrual cycle in the last year. The exclusion criteria were indications for pelvic surgery, a history of pelvic surgeries or caesarean sections, endometriosis, current use of hormonal contraceptives, a fixed uterus or pelvic masses.

All the participants completed a questionnaire, which included questions on pain during the menstrual cycle, including premenstrual pain and dysmenorrhoea, and dyspareunia during sexual activity. The participants were asked whether dysmenorrhoea required them to take pain relief medication and whether dyspareunia restricted sexual activity. Demographic characteristics (age and body mass index [BMI]), were recorded, as well as information on gravidity, parity and infertility. The intensity of pain symptoms was evaluated using a visual analogue scale (VAS).

To determine the position of the uterus and diagnose uterine retroversion, all the participants underwent a pelvic examination and transvaginal ultrasound. Two physicians performed all the examinations. Of the 133 participants included in the study, 61 women had a retroverted uterus, and 72 women had an anteverted uterus (control group). All 133 women had successful pregnancies. The mode of delivery was recorded. (After completion of the records, the patients were divided into two groups: a retroverted group (group 1, n: 61) and an anteverted group (group 2, n: 72.) The recorded parameters in the two groups were then compared.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). The Kolmogorov–Smirnov test was used to determine the normality of the data distribution. Categorical variables were expressed as percentages (%) and counts (n). Continuous values were given as mean ± SD. The continuous variables were analysed using an independent T-test, and a chi-square test was used to determine associations between the categorical variables. A p value of < 0.05 was considered statistically significant.

RESULTS

Of 153 premenopausal women who visited the department for pregestational counselling, twenty women were excluded for the following reasons: endometriosis (n = 9), a history of pelvic surgery (n = 3), a fixed uterus (n = 2) and pelvic or adnexal masses (n = 6). Thus, the final study group included 133 women.

There was a statistically significant difference between the two groups in the incidence of dyspareunia and dysmenorrhoea, BMI, recurrent pain,ovulation-related pain, premenstrual pain, restriction of sexual activity due to dyspareunia, analgesic drug use for dysmenorrhoea, and mode of delivery ($p < 0.05$). There was no significant difference between the two groups in terms of premenstrual syndrome, heights, gravidity or parity ($p > 0.05$) (Table 1). The results of the independent T-test revealed significantly higher weights and BMI among the women with a retroverted uterus as compared with those of the women with an anteverted uterus. According to the VAS scores, the frequency and severity of dyspareunia were significantly higher among women with a retroverted uterus than among those with an anteverted uterus ($p < 0.05$).

The rate of cyclic pain among the retroverted uterus group (82%) was statistically higher than that among than anteverted uterus group (30.6%) (p<0,005). The incidence of ovulation-related pain in the retroverted uterus group was statistically lower (3.3%) than that in the anteverted uterus group (22.2%),(p<0,005). The incidence of premenstrual pain in the retroverted uterus group was statistically lower than that in the anterverted uterus group (3.3% vs. 36.1%). The incidence of analgesic drug use for dysmenorrhoea was statistically higher in the retroverted uterus group (82%) than in the anteverted uterus group (5.6%),(p<0,005). In the retroverted uterus group, dyspareunia restricted sexual activity at a higher rate (83.6%) than in the anteverted uterus group (4.2%),(p<0,005). There was no association between uterine retroversion and premenstrual syndrome, height, gravidity and parity (p>0,005).

In the retroverted uterus group, 70.8% of women had an emergency caesarean section, whereas only 31% of women in the anteverted group had an emergency caesarean section. There was no statistically significant difference between the rates of patients who did not give birth in the two groups.

Table 1: Descriptive Statistics and Analysis Results in Comparing Variables by Patient Groups

		Retroverted Uterus (N=61)	Anteverted or Intermediary Uterus (N=72)	p value
Dyspareunia VAS score	0	3 (%4,9)	31 (%43,1)	b0,000*
	1-3	5 (%8,2)	23 (%31,9)	
	4-7	26 (%42,6)	17 (%23,6)	
	8-10	27 (%44,3)	1 (%1,4)	
Dysmenorrhea VAS score	0	2 (%3,3)	31 (%43,1)	b0,000*
	1-3	17 (%27,9)	23 (%31,9)	
	4-7	23 (%37,7)	18 (%25)	
	8-10	19 (%31,1)	0 (%0)	
PMS	+	26 (%42,6)	37 (%51,4)	b0,313
	-	35 (%57,4)	35 (%48,6)	
Height (Cm)		162,0 ± 7,1	162,8 ± 6,3	a0,493
Weight (kg)		74,3 ± 10,4	69,7 ± 10,9	a0,015*
Body mass index kg/cm2		28,4 ± 3,7	26,3 ± 4,0	a0,002*
Gravid	1	12 (%19,7)	18 (%25)	b0,761
	2	25 (%41)	29 (%40,3)	
	3	15 (%24,6)	13 (%18,1)	
	4	9 (%14,8)	12 (%16,7)	
Parity	1	14 (%23)	25 (%34,7)	b0,271
	2	27 (%44,3)	30 (%41,7)	
	3	20 (%32,8)	17 (%23,6)	
Cyclic pain	-	11 (%18)	50 (%69,4)	b0,000*
	+	50 (%82)	22 (%30,6)	
Ovulation pain	-	59 (%96,7)	56 (%77,8)	b0,001*
	+	2 (%3,3)	16 (%22,2)	
Premenstrual pain	-	59 (%96,7)	46 (%63,9)	b0,000*
	+	2 (%3,3)	26 (%36,1)	
Dysmenorrhea requires medical treatment	-	11 (%18)	68 (%94,4)	b0,000*
	+	50 (%82)	4 (%5,6)	
Dyspareunia restricts sexual activity	-	10 (%16,4)	69 (%95,8)	b0,000*
	+	51 (%83,6)	3 (%4,2)	
Delivery type	No delivery	8 (%16,7)	10 (%13,9)	b0,000*
	Normal vaginal delivery	6 (%12,5)	50 (%69,4)	
	Primary cesarean delivery	34 (%70,8)	12 (%16,7)	

* p<0,05; a Independent Group t Testi; b Ki-Square Test

DISCUSSION

A retroverted uterus is diagnosed as a uterus with an angle between the axis of the uterine body and the vagina, with the body directed posteriorly towards the hollow of the sacrum [6]. In women who present with pelvic pain, an ultrasound scan is generally performed to help determine the cause. To diagnose a retroverted uterus, the

bladder must be empty at the time of scanning. [6, 7]. In the present study, the incidence and severity of dyspareunia and dysmenorrhoea were significantly associated with uterine retroversion in premenopausal women. A similar study to ours reported a comparable rate of dyspareunia and pelvic pain symptoms with 581 participant [18]. No previous studies have examined the effects of uterine retroversion on delivery modes (i.e. vaginal vs. caesarean deliveries). According to the results of our study, uterine retroversion is a common reason for a caesarean section.

Several recent studies reported that uterine retroversion may lead to uterine incarceration, which resulted in severe and progressive complications, such as recurrent urinary tract infections, acute urinary retention, anterior uterine wall thinning due to uterine sacculation, bladder rupture, preterm labour, premature rupture of foetal membranes, spontaneous abortions and uterine rupture during labour. Uterine rupture in cases of uterine incarceration was attributed to failure of the cervix to dilate during labour [19]. If it is not diagnosed, it can lead to intrauterine growth retardation and oligohydramnios. In such cases, an emergency caesarean section, with bladder, cervical, vaginal, and posterior or anterior uterine wall incisions may be required, all of which have the potential for renal failure and sep¬sis [20]. In a pregnant patient with an incarcerated uterus, uterus continues to grow/ enlarge between the subpromontory sacrum and pubis in the pelvic cavity [8]. Potential causes of an incarcerated gravid uterus, which is diagnosed in approximately 1 in every 3,000 pregnancies, include uterine anomalies, fibroids, pelvic adhesions, endometriosis or a deep sacral cavity with a prominent promontory [8]. In most cases, a retroverted uterus undergoes spontaneous correction to an anteverted uterus by the first trimester [9]. An incarcerated gravid uterus is generally diagnosed by a pelvic examination and confirmed by transvaginal ultrasound on an empty bladder [6, 7]. A caesarean section should be planned if uterin reduction cannot be performed [8, 10–14]. Preoperative diagnosis and treatment of incarceration are essential to avoid intraoperative complications and trauma to the bladder, vagina and cervix during labour and to avoid the need for a transvaginal caesarean section and a hysterectomy [10, 14–17].

In the present study, there was an increased rate of caesarean sections in the retroverted uterus group. The most frequent indication for a caesarean section in the retroverted uterus group was prolonged labour, whereas it was cephalopelvic disproportion in the anteverted uterus group. In cases of uterine retroversion, acceleration of uterine contractions during vaginal labour is attributed to a decrease in blood flow due to the position of the uterus.

The mechanisms by which uterine retroversion cause pelvic pain are unclear. According to some research, it may be due to the penis colliding with the corpus of the uterus during intercourse or retroversion forcing the cervix to move anteriorly during intercourse instead of as a unit with the uterosacral ligaments, with resulting stretching of the ligaments [21]. According to other research, pelvic venous congestion in uterine retroversion may contribute to pain and venous insufficiency during labour and lead to an emergency caesarean section.

Recent research showed that an anteverted retroflexed uterus was extremely rare and that it was a consequence of caesarean delivery [22]. The authors reported that the retroverted uterus turned into anteversion after a caesarean section but remained in the retroflexion due to the adhesion tension in the caesarean scar in the lower segment of the uterus [22].

Our study had a number of limitations. One limitation was that we did not investigate the relation between uterine retroversion and pregnancy outcomes, such as birth weights and perinatal mortality To the best of our knowledge, no studies have investigated the relationship between uterine retroversion and mode of delivery previously. Another limitation was that ultrasound cannot detect superficial endometriosis. The prevalence of superficial endometriosis as a confounding factor may be as high as 50% in unselected populations [23, 24]. Undetected intra-abdominal lesions due to endometriosis may also have accounted for some cases of uterine retroversion and retrograde menstruation. Nevertheless, the present study may contribute to national data and/ or the systematic reviews and meta-analyzes [25]

and which will be done together with other studies originating from our country.

CONCLUSIONS

To the best of our knowledge, this is the first study specifically designed to evaluate the effect of uterine retroversion on pelvic pain and delivery type in a general population of women admitted for pregestational counselling. In this study, uterine retroversion was a common cause of pelvic pain and primary caesarean sections. Further studies are needed to confirm these findings. Nevertheless, the data in the present study shed light on the association of the anatomical status of the uterus with pelvic pain and delivery type.

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RESEARCH ARTICLE

ARAŞTIRMA

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The relationship between contrast associated acute kidney injury and direct bilirubin levels

Kontrast ilişkili akut böbrek hasarı ve Direkt Bilirubin Düzeyleri Arasındaki İlişki

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ABSTRACT

Aim: In this study we aimed to association between bilirubin levels, which is known to have anti-oxidative, anti-inflammatory and anti-thrombotic effects, and contrast associated acute kidney injury (CA-AKI) in patients with acute coronary syndrome (ACS).
Methods: Between 2017-2020, consecutive patients over 18 years of age who applied percutaneous angioplasty with the ACS diagnosis and met the exclusion and inclusion criteria (n:514) were retrospectively screened. Age, gender, chronic diseases and complete blood count parameters of the cases were recorded. Biochemical parameters, before applying contrast and 48 hours after applying contrast, were recorded. A 25% increase in creatinine level measured 48 hours after contrast application compared to basal creatinine was defined as CA-AKI.
Results: CA-AKI rate was higher in females(p=0.011). In the CA-AKI positive patient group, the mean age was found significantly higher (p=0.04), hemoglobin (p=0.007), direct bilirubin (p=0.008) levels were found significantly lower. Direct bilirubin was found to be a predictor as a result of our statistical analysis to identify independent predictors of CA-AKI (Beta:0.051 OR 95% CI:0.007-0.392, p=0.004). It was found that the direct bilirubin value of 0.065 predicted CA-AKI with 90% sensitivity and 91% specificity.
Conclusions: It was observed that the direct bilirubin values were significantly lower in the CA-AKI positive patient group, and the direct bilirubin value of 0.065 predicted CA-AKI with 90% sensitivity and 91% specificity.

Keywords: contrast associated acute kidney injury; direct bilirubin; bilirubins

ÖZ

Amaç: Bu çalışmada akut koroner sendromlu (AKS) hastalarda antioksidatif, anti-inflamatuar ve antitrombotik etkileri olduğu bilinen bilirubin düzeyleri ile kontrast ile ilişkili akut böbrek hasarı (KI-ABH) arasındaki ilişkiyi araştırmayı amaçladık.
Yöntemler: 2017-2020 tarihleri arasında AKS tanısı ile perkütan anjioplasti yapılan, dışlama ve dahil edilme kriterlerine uyan ardışık 18 yaş üstü hastalar (n:514) retrospektif olarak tarandı. Hastaların yaş, cinsiyet, kronik hastalıkları, tam kan sayımı parametreleri, kontrast öncesi ve kontrast verildikten 48 saat sonraki biyokimyasal parametreleri kaydedildi. Kontrast ile ilişkili akut böbrek hasarı tanısı kontrast uygulandıktan 48 saat sonraki serum kreatininde bazal kreatinine göre %25 artış olarak tanımlandı.
Bulgular: Kadınlarda KI-ABH oranı daha yüksek bulundu (p=0.011). Hastalar KI-ABH pozitif ve negatif olmak üzere iki gruba ayrıldı. KI-ABH pozitif hasta grubunun yaş ortalaması anlamlı olarak daha yüksek (p= 0.04), Hemoglobin (p=0.007) ve direkt bilirubin (p=0.008) düzeyleri anlamlı olarak daha düşük bulundu. KI-ABH'nın bağımsız öngördürücüleri tespit etmek amacıyla yaptığımız istatistiksel analizi sonucunda direkt bilirubin (Beta: 0,051 OR (95% CI 0,007/0,392 p=0,004) bir öngördürücü olarak bulundu. Direkt Bilirubin 0.065 değerinin %90 sensivite ve %91 spesivite ile KI-ABH 'nı öngördürdüğü tespit edildi.
Sonuçlar: KI-ABH pozitif hasta grubunda direkt bilirubin düzeylerinin anlamlı olarak daha düşük olduğu ve Direkt Bilirubin 0.065 değerinin %90 sensivite ve %91 spesivite ile KI-ABH 'nı öngördürdüğü bulunmuştur.

Anahtar Kelimeler: Kontrast ile ilişkili akut böbrek hasarı (KI-ABH); direkt bilirubin; bilirubinler;

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INTRODUCTION

The incidence of contrast associated acute kidney injury (CA-AKI) in the normal population is 1-2% and the incidence in the patient group with risk factors is 50% [1]. It has been reported that 13% of all CA-AKI cases occur secondary to the use of contrast agent [2]. CA-AKI increases the length of hospitalization and has negative effects on morbidity and mortality [1]. The contrast agent increases the release of inflammatory markers, induces the production of various mediators that increase vasoconstriction in the renal medulla and reduces vasodilation, ultimately causing hypoxia, acute tubular necrosis and acute kidney injury [3]. It is also known that oxidative stress plays an important role in the development of CA-AKI [1].

Bilirubin mainly occurs as a result of the breakdown of the erythrocytes that have expired and the destruction of the heme proteins in the erythrocytes. Indirect bilirubin is converted to direct bilirubin in hepatic cells and direct bilirubin is excreted with bile. Previously, bilirubin was known as a waste product, but it is now known to be an anti-oxidative, anti-inflammatory and anti-thrombotic [4, 5]. Different results have been found in studies to show the association between bilirubin and diseases. It was shown in a study that an inverse relationship exists between total bilirubin and cardiovascular disease risk. In another study, in patients with acute coronary syndrome (ACS), total bilirubin and direct bilirubin have been shown to predict long-term adverse events [5]. In yet another study, it was stated that in heart failure patients, bilirubin predicts a poor prognosis in decompensated heart failure [6]. Other reports have shown that mild bilirubin elevation may protect against all-cause mortality and cardiovascular disease. There are findings in the literature that bilirubin protects from kidney damage [7]. In this research it was aimed to investigate the relationship between bilirubin levels and CA-AKI in patients who applied coronary angiography.

METHODS

Between 2017 and 2020, the files of 514 patients over the age of 18 who applied primary percutaneous coronary intervention (P-PCI) with ACS were analyzed retrospectively. Age, gender, chronic diseases and complete blood count (CBC) parameters of the cases were recorded. Biochemical parameters, before applying contrast and 48 hours after applying contrast, were documented and it was evaluated whether CA-AKI developed in the patients. Patients with allergies to contrast agents, cardiogenic shock, hematological disease, chronic inflammatory or autoimmune disease, those using oral anticoagulants, those with creatinine clearance <60 mL / min and those with chronic renal failure requiring dialysis were all excluded from the study. It was approved by the Ordu University Clinical Research Ethics Committee (2020/163).

Definitions: Acute coronary syndrome diagnosis was made with typical increase or decrease in cardiac troponins together with evidence of myocardial ischemia, according to the myocardial infarction diagnostic criteria [7][8]. Patients were classified as ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA), in accordance with ischemic electrocardiographic changes and clinical findings.

P-PCI was administered to all these patients within the first 12 hours after the onset of chest pain. Before the procedure, all patients were given 300 mg aspirin and 600 mg clopidogrel or 180 mg ticagrelor loading dose, standard heparin and 10.000 U i.v. After the P-PCI procedure, all patients were given acetylsalicylic acid 100 mg / day and clopidogrel 75 mg / day or ticagrelor 180 mg / day and subcutaneous enoxapine 1 mg / kg twice a day. For patients undergoing P-PCI, iopromide (Ultravist®) was used as the non-ionic iso-osmolar contrast agent. All patients were hydrated (0.9% sodium chloride 1 ml / kg / hour) via intravenous route for 12 hours after the intervention. The term contrast-induced nephropathy is usually defined as a serum creatinine rise of 25% or 0.5 mg/dl occurring approximately 2–5 days after contrast exposure [9].

The mean of two blood pressure measurements of the patients was taken. Mean blood pressure results above 140/90 mmHg or those patients using anti-hypertensive drugs, were defined as hypertension. Diabetes mellitus was defined as at least two fasting blood glucose levels above 126

mg / dl or the use of antidiabetic agents. CA-AKI was diagnosed 48-72 hours after intravascular contrast administration, with an increase in serum creatinine > 25% relative to basal creatinine, or an absolute increase in serum creatinine of at least 44 µmol / L (0.50 mg / dl) [8] [10].

Blood sampling analysis: Blood samples were taken before P-PCI treatment and 48 hours after PCI treatment. Complete blood count and urea creatinine were studied from blood samples. The creatinine clearance was calculated using the MDRD (Modification of Diet in Renal Disease study) GFR= 186 X ([Scr] -1.154) X ([Age] -0.203) X (0.742 if woman). Biochemical parameters were analyzed using the ARCHITECT c8000 clinical analyzer (Abbott, IL, USA). A CELL-DYN Ruby automated hematology analyzer (Abbott, IL, USA) was used for hemogram parameters.

Statistical analysis: The Shapiro Williams-W Normality Test was applied to evaluate the distribution of the data. Homogeneity control of group variances was done by with the Levene Test. Homogeneously distributed data were compared with the Student T test and non-homogeneously distributed data with the Mann-Whitney U test. The Chi-square test was used for categorical variables; if a cell had an expected frequency below 5, the likelihood ratio chi-square value was used instead of Pearson chi-square value. Numerical variables were expressed as median (minimum and maximum) and mean ±SD and categorical variables were given as percentages. The parameters predicting CA-AKI were evaluated via Binary Logistic regression analysis. ROC curve analysis was performed to find the cut off value of direct bilirubin, which predicted CA-AKI. The SPSS 25.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. A P<0.05 value was considered statistically significant.

RESULTS

In comparison of CA-AKI positive and negative patients groups, with respect to chronic diseases, no significant difference was found between the groups (p> 0.05). When compared in terms of gender and the rate for women, there were more female patients in the CA-AKI positive group (29.9%) (p = 0.011) (Table 1).The median age of the CA-AKI positive patient group was found to be significantly higher (p = 0.04). Also, ALP (p = 0.013) was significantly higher and GGT (p = 0.013), albumin (p = 0.020), hemoglobin (p = 0.007) and direct bilirubin (0.008), were significantly lower in CA-AKI positive patient group (Table 2).

Table 1: Comparison of Gender And Chronic Diseases

	CA-AKI (-) n=347	CA-AKI (+) n=167	P Value
Gender			
Male (n,%)	278 (80,1)	117 (70,1)	0,011
Female (n,%)	69 (19,9)	50 (29,9)	
Diabetes Mellitus (n,%)	85 (24,5)	49 (29,3)	0,241
Hypertension (n,%)	138 (39,8)	76 (45,5)	0,216
Coronary Artery Disease (n,%)	85 (45,7)	49 (36,6)	0,102
Heart Failure (n,%)	45 (13)	27 (16,2)	0,328
Cerebrovascular Accident (n,%)	17 (9,1)	11 (8,3)	0,780
Hyperlipidemia (n,%)	10 (5,4)	7 (5,3)	0,959
Chronic Renal Failure (n,%)	6 (3,2)	4 (3)	0,903
Chronic Obstructive Pulmonary Disease(n,%)	14 (7,5)	10(7,5)	0,983

Table 2: Comparison of Blood Parameters

	CA-AKI (-) n=347	CA-AKI (+) n=167	P Value
Age (year)	61,48±12,27	64,90±13,6	0,040
Blood Urea Nitrogen, mg/dl	18,2 (7,50-71)	17,3	0,226
Pre-contrast Creatinine, mg/dl	0,9 (0,42-5,1)	0,8 (0,4-2,9)	0,000
Post-contrast Creatinine, mg/dl	0,9 (0,40-5,1)	1,3 (0,65-7)	0,000
Pre-contrast GFR, ml/dk/1.73m2	87,67(11,47-175,23)	88,71(16,72-162,42)	0,213
Post-contrast GFR, ml/dk/1.73m2	87,29(11,47-197,89)	57,14(6,17-102,19)	0,000
Aspartate Aminotransferase, U/L	35 (10-648)	40 (11-550)	0,119
Alanine Aminotransferase, U/L	25 (5-1225)	27 (5-368)	0,240
Alkaline Phosphatase, U/L	85 (32-1120)	91 (29-296)	0,013
Gamma Glutamyl Transferase,U/L	33 (3-555)	27 (3-487)	0,013
Lactate Dehydrogenase,U/L	326 (167-2156)	341 (176-1468)	0,249
Total bilirubin, mg/dl	0,52 (0,02-4,80)	0,58(0,06-2,37)	0,546
Direct bilirubin, mg/dl	0,12 (0,00-3,30)	0,10 (0,01-0,72)	0,008
Total protein, g/dl	7,13±0,69	7,17±0,62	0,657
Albumin, g/dl	4,07±0,47	3,98±0,43	0,030
glucose, mg/dl	136 (70-795)	132 (11-561)	0,455
Hemoglobin, g/dl	15,47±2,03	14,96±2,02	0,007
White blood cell 10*3/U/L	10,83(3,40-46,9)	11,09 (4,7-28,8)	0,870
Platelet, 10*3/U/L	240 (8,4-934)	239 (6-592)	0,442
C reactive protein, mg/L	4,21(0,97-114)	4,56 (2,97-130)	0,360

As a result of the Binary Logistic regression analysis performed to find independent predictors of CA-AKI, age (Beta: 1.022 OR 95% CI: 1.003-1.041, p = 0.021) and direct bilirubin (Beta: 0.051 OR 95% CI: 0.007-0.392, p = 0.004) were found to be independent predictors (Table 3). The direct bilirubin value of 0.065 predicted CA-AKI with 90% sensitivity and 91% specificity (AUC: 0.576, 95% CI: 0.571-0.630, p=0.09) (Figure 1). When the correlation between Bilirubins and Blood Urea Nitrogen, Post-Contrast Creatinine, Post-Contrast GFR is examined no significant relationship was found.

Table 3 Investigation of CA-AKI 's Independent Predictors with Binary Logistic Regression Analysis

	Beta	OR (%95 Cl)	P
Age	1,022	1,003/1,041	0,021
Hemoglobin	0,937	0,833/1,055	0,283
ALP	1,005	0,999/1,010	0,113
GGT	0,999	0,994/1,003	0,628
Albumine	0,839	0,514/1,370	0,484
Direct bilirubin	0,051	0,007/0,392	0,004

ALP:Alkaline Phosphatase, GGT:Gamma Glutamyl Transferase

DISCUSSION

In this study, CA-AKI rate (29.9%) in women and the mean age of CA-AKI positive patient group were found to be significantly higher (p = 0.011 and p = 0.04, respectively). Also, direct bilirubin was significantly lower in CA-AKI positive patient group (p = 0.008). As a result of analysis to find independent predictors of CA-AKI, age and direct bilirubin were found to be independent predictors. It was shown that direct bilirubin predicted CA-AKI with 90% sensitivity and 91% specificity at 0.065 level.

As has been shown, the contrast agent has a direct toxic effect on the endothelium, reducing renal medullary blood flow and causing renal artery vasoconstriction, causing renal ischemia and kidney damage [7]. Free radicals, which have been shown to be involved in the pathophysiology of many diseases, are becoming more and more important. Antioxidants and free radicals are in balance in healthy individuals, however when this balance is altered in favor of free radicals, oxidative stress is observed, and diseases occur. One of the most important causes of CA-AKI formation is oxidative stress resulting from hypoxia [1]. Reactive oxygen species (ROS) are formed by oxidative stress. These are superoxide (O2-), hydrogen peroxide (H2O2) and hydroxyl radicals (OH-). O2- captures nitric oxide (NO) rapidly and renal microcirculation is disrupted as a result of the decrease in NO level. At the same time, ROS activates vasoconstrictor substances (such as angiotensin 2, thromboxane A2, endothelin 1, adenosine and norepinephrine) by creating extracellular signals [1]. Contrast media inhibits mitochondrial enzyme activities and then increases adenosine through hydrolysis of ATP. Both adenosine catabolism and medullary hypoxia produce ROS that scavenges NO [3].

Bilirubin, albumin, uric acid, transferrin, ceruloplasmin etc. are known as endogenous antioxidants [11,12]. It has been reported in the literature that bilirubin was a cytotoxic metabolite causing brain damage at high concentrations, while it acts as an endogenous antioxidant at low concentrations [13,14]. Experimental studies have shown that bilirubin has antioxidant properties such as scavenging ROS and inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity. It has been stated that this causes a decrease in oxidative stress [15].

Ischemia-perfusion damage resulting from restoration of blood flow after tissue ischemia leads to endothelial cell apoptosis, inflammation and organ dysfunction. Increase in bilirubin reduces ischemia-perfusion damage in organs. Bilirubin also increases endothelial function with its antioxidant effect [7].

It has been shown in studies that serum bilirubin could be a biomarker of many other diseases [16]. He et al. found that bilirubin levels were significantly lower in patients with lupus nephritis compared to controls, and the bilirubin level increased after steroid therapy was given to these patients and the amount of protein in 24-hour urine decreased [16]. In another publication, it was mentioned that patients with mild elevations in unconjugated bilirubin serum levels had a much lower prevalence / incidence of coronary heart and peripheral vascular diseases [17]. Li et al. showed that bilirubin (TBil, DBil and IBil) levels were low in patients diagnosed with pemphigus vulgaris and were associated with disease

severity [18]. Demir et al. observed that bilirubin levels were lower in patients with coronary artery ectasia than in the control group [19]. It has been stated that there is an inverse correlation between bilirubin and coronary artery disease, whose pathophysiology involves lipid oxidation and the formation of oxygen radicals. In addition, Erkan et al. reported that bilirubin could be protective against atherosclerosis as a result of their study [20].

The important limitations of our study were that the study was single centered, the number of patients was insufficient and only one antioxidant parameter was examined. The amount of applied contrast substance and duration of process (Primary percutaneous coronary intervention (P-PCI)) were not included in the study because they were not recorded in the files. Also, echocardiography findings of all patients were not recorded as the patients were evaluated in the emergency clinic.

In view of the results of this study, bilirubin levels can be used as an independent risk factor to predict the development of after P-PCI contrast nephropathy. It is known that many different pathological mechanisms coexist in the emergence of contrast nephropathy. It is not known which pathophysiological mechanisms are more dominant in which patient. Taking preventive measures before applying contrast can reduce the development of CA-AKI. As itt is known that there is no specific treatment once CA-AKI develops, it is clear that preventive measures are required, especially in patients with high risk of developing CA-AKI. According to these results, we believe that administration of treatments with antioxidant properties may be worthy of further investigation in the prevention or early intervention of CA-AKI.

CONCLUSIONS

It was found that the direct bilirubin levels were significantly lower in the CA-AKI positive patient group and the direct bilirubin value of 0.065 predicted CA-AKI with 90% sensitivity and 91% specificity.

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The relationship between speech difficulties and brain laterality in Attention Deficit Hyperactivity Disorder and Specific Learning Disorder

Dikkat eksikliği ve Hiperaktivite Bozukluğu ve Özgül Öğrenme Bozukluğunda Beyin Lateralitesinin Konuşma Problemleri ile İlişkisi

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ABSTRACT

Aim: We aimed to examine the behavioral determinants of brain laterality and their associations with speech difficulties in children with Attention Deficit Hyperactivity Disorder (ADHD) and Specific Learning Disorder (SLD).
Methods: This cross-sectional study was conducted with a clinical sample of 7-18 years old patients with ADHD and/or SLD diagnosis. Patients' sociodemographical, developmental and medical information were taken during their clinical interviews. Behavioral determinants of brain laterality were assessed by several motor tasks. These tasks were "handwriting" for handedness, "looking through the telescope" for eyedness, and "hitting the ball or standing on one foot" for footedness.
Results: A total of 130 patients participated in the study. Left side preference and crossed laterality were common in patients with SLD (with or without comorbid ADHD) but not in patients with pure ADHD. Left eyedness/footedness were associated with speech disorders (p<0,05).
Conclusions: This study has shown that even after controlling for other factors affecting the development of brain laterality SLD, but not ADHD, is associated with left-sided preference and cross laterality. The relationship between speech disorders and left-eyedness/footedness in ADHD and SLD patients suggests that development of brain laterality is actually mediated by speech development.

Keywords: ADHD, SLD, brain laterality, speech disorders

ÖZ

Amaç: Bu çalışmada Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) ve Özgül Öğrenme Bozukluğu (ÖÖB) tanıları olan çocuklarda beyin lateralitesinin davranışsal belirteçleri ve bunların konuşma problemleri ile ilişkisinin incelenmesi amaçlanmıştır.
Yöntemler: Bu kesitsel çalışma DEHB ve/veya ÖÖB tanılarına sahip 7-18 yaşındaki hastalardan oluşan klinik bir örneklem ile yürütülmüştür. Hastaların sosyodemografik, gelişimsel ve medikal bilgileri klinik görüşme sırasında alınmıştır. Beyin lateralitesinin davranışsal belirteçleri çeşitli motor görevler ile değerlendirilmiştir. Bu görevler el tercihi için "kalem ile yazma", göz tercihi için "teleskoptan bakma", ayak tercihi için "topa vurma" veya "tek ayak üzerinde durma" idi.
Bulgular: Çalışma DEHB ve/veya ÖÖB tanısı olan toplam 130 hasta ile tamamlanmıştır. Sol el-göz ve ayak tercihi ve çapraz lateralite ÖÖB (komorbid DEHB olsun veya olmasın) tanısı olan hastalarda sık iken sadece DEHB tanısı olanlarda değildi. Sol göz/ayak tercihi konuşma bozuklukları ile ilişkili idi (p<0,05).
Sonuçlar: Bu çalışma beyin lateralitesini etkileyen diğer faktörlerin kontrol edilmesinden sonra bile DEHB'nin değil ama ÖÖB'nin sol-yan tercihi ve çapraz lateralite ile ilişkili olduğunu saptamıştır. DEHB ve ÖÖB olan hastalarda konuşma bozuklukları ve sol göz/ayak tercihi arasındaki ilişkiyi gösteren diğer bulgumuz ise bu bozukluklardaki beyin lateralitesinin gelişimine aslen konuşma gelişiminin aracılık ettiğine işaret etmektedir.

Anahtar Kelimeler: DEHB, ÖÖB, beyin lateralitesi, konuşma bozuklukları

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) and Specific Learning Disorder (SLD) are among the common psychiatric disorders of childhood [1]. Recently, the Turkey Epidemiology Study has shown that the prevalence of ADHD and SLD in children is 12,4% and 0,5%, respectively [2]. The two disorders frequently coexist with each other, and genetic and environmental factors play leading role in their etiology. Although their pathophysiologies have not been fully understood yet, right hemisphere dysfunction and atypical cerebral asymmetry have been demonstrated in both ADHD and SLD patients [3,4].

Hemispheric asymmetries are required for the functional organization of the human brain. In the vast majority of people, the motor areas, the posterior (sensory) speech center (Wernicke's field) and the anterior (motor) speech center (Broca's field), are generally better developed in one of two hemispheres. This better developed hemisphere, so called the dominant hemisphere, is the left one in 90% of people [5]. Atypical asymmetry, moving away from the typical laterality pattern, indicates pathological changes in the left and right hemispheres and/or in between hemispheres [3]. Besides the ADHD and SLD, atypical brain lateralization has been shown in several other psychiatric disorders including speech disorders (SD) which are frequently coexist with especially SLD [6].

Hand, eye, ear and foot preferences are the behavioral measurements of brain laterality. Since it is inexpensive and easy, handedness is often used as an indicator of cerebral lateralization in clinical settings [7]. Handedness is correlated with cerebral asymetries, and right handedness refers to left brain dominance [8]. Although most of the people in society have right-handedness, some are left-handed. Moving away from right-handedness has been associated with schizophrenia [9], autism [10] as well as SD, such as stuttering [11]. Handedness is also influenced by gender (higher incidence of left-handedness in males), genetics and intrauterine posture [5]. Moreover, laterality and associated handedness influenced by conditions including birth complications [12], neurodevelopmental disorders, obsessive-compulsive disorder [13] and medical conditions such as epilepsy and autoimmune disorders [14]. Increased rates of left handedness have been shown in some autoimmune and inflammatory diseases and also in hearing loss [5]. In general, a right-handed person is expected to have right eye/ear/foot preferences. However, in some people at least one of the hand, eye, ear and foot preferences is different from the others, which is defined as crossed laterality.

Studies on ADHD and SLD present inconsistent findings related to handedness in the affected children. This may be related to differences in sample selection among studies. To the best of our knowledge, studies have been mainly conducted on a single disorder, and there is no information about whether coexisting developmental disorders (including speech problems) or medical conditions related to atypical brain laterality, are excluded. In this study, we aimed to examine brain laterality and its relationship with speech difficulties in patients with pure ADHD, pure SLD and Comorbid ADHD + SLD, in the absence of any chronic medical disease, birth complications, neurodevelopmental disorder or major psychiatric/neurological disorder. We hypothesized that left side preferences and crossed laterality were common in all groups. We also hypothesized that speech difficulties (SD and speech delay) were more common in SLD patients and they were related to left side preference and crossed laterality in other words atypical brain laterality.

METHODS

Children aged 7 to 13 who were followed up with ADHD and/or SLD diagnoses from the child psychiatric outpatient clinic were included in the study. Children with other comorbid psychiatric disorder (other than SD) including Autism Spectrum Disorder, Anxiety Disorder, Mood Disorder, Psychotic disorder, Tic Disorder, medical disorders including congenital/acquired neurological disease, chronic physical illness, birth complications and vision or hearing impairments, were all excluded from the study. Each patient was assessed with standardized intelligence tests and those with a total score of at least 80 were included in the study.

All participants were evaluated by clinical

psychiatric examination based on DSM-5. Individual and parental sociodemographic information of the patients were questioned during clinical interview and recorded in the data form created by the researchers. During the same interview, each child was asked to participate in a series of motor tasks to determine their handedness, eyedness and footedness. For handedness “the hand preferred in handwriting”, for eyedness “the eye used when looking through telescope”, and for footedness “the foot used when hitting the ball or standing on one foot” were used. When crossed laterality was detected, it was recorded on the data form. The study was approved by the local ethics committee of a training and research hospital protocol number 2019/190 and was performed in accordance with the ethical standards established in the Helsinki Declaration, 1989. All participants and their parents were informed about the study and their written and verbal consents were received.

Data form: It was formed to get information related to child's gender, age, history of speech delay (starting to use sentences after 3 years of age), time of delivery (term, pre-term, post-term) and exposure to tobacco smoke during intrauterine or postnatal period, current SD (stuttering or articulation disorder) and parental educational status, family history of SLD and speech delay in the first or second degree relatives.

Statistical Analysis: For evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio), the Shapiro-Wilk test and boxplot graphics were used for variables with normal distribution. The Student T test was used for intergroup comparisons of normally distributed variables. The Pearson Chi-Square test and Fisher-Freeman Halton test were used for comparison of qualitative data. Significance was evaluated at the $p < 0.05$ level. NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used for statistical analysis.

RESULTS

A total of 130 children with a mean age of 8.88 ± 1.34 years (age range 7 to 13 years) participated in this study. Of them 45 had pure SLD (SLD Group), 30 had pure ADHD (ADHD Group) and 55 had comorbid ADHD + SLD (Comorbid Group).

Patient groups were similar in terms of age, gender and monthly family income. Groups differed in terms of the parental education levels, family history of SLD and speech delay, and this difference was due to the ADHD group. Compared to the other two groups, the ADHD group had higher parental educational levels, and lower rates of family history of speech delay and SLD ($p < 0.05$) (Table 1).

The groups differed significantly in terms of speech delay history and SD rates. In the SLD group and Comorbid group, speech delay (44,4% and 47,3% respectively) and SD (42,2 % and 34,5% respectively) were very common. In the ADHD group the ratios of delayed speech (10%) and SD (none) were significantly lower than the other two groups ($p < 0.05$) (Table 2).

In the SLD group left handedness was present in 26,7 % (n=12), left eyedness was present in 42,2 % (n=19), left footedness was present in 22,2 % (n=10) and crossed laterality was present in 33,3 % (n=15) of patients. These ratios were 20% (n=11), 43,6 % (n=24), 20 % (n=11) and 40% (n=22) in the Comorbid group. Compared to the other two groups, the ADHD group had higher ratios for right handedness, eyedness and footedness and lower ratio of crossed laterality ($p < 0.05$) (Table 3). Handedness, eyedness, footedness and crossed laterality were not related to speech delay ($p > 0.05$). Left handedness-eyedness-footedness and crossed laterality were higher in patients with SD, but the rate of left eyedness and left footedness were statistically significantly higher among patients with SD ($p < 0.05$) (Figure 1).

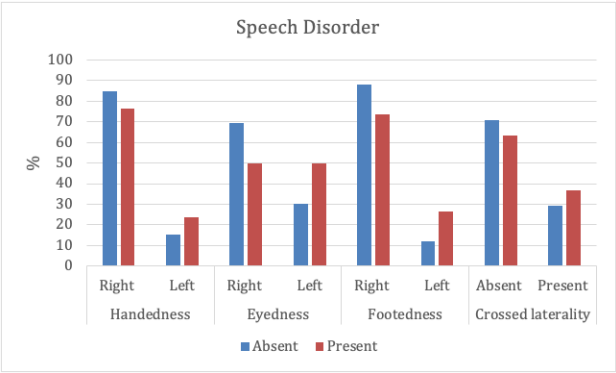

Figure 1: Examination of relationship between the behavioral indicators of laterality and speech disorder in participants

Table 1: Comparison of groups according to demographic characteristics of participants

		Total	SLD- Group	ADHD Group	Comorbid Group	P
Age	Mean ±SD	8,88 ±1,34	8,73 ±1,29	9,07 ±1,31	8,91 ±1,41	[a]0,520
	Min-Max (Median)	7-13 (9)	7-12 (9)	7-12 (9)	7-13 (8)	
		N(%)	N(%)	N(%)	N(%)	
Gender n(%)	Girls	38 (29,2)	11 (24,4)	9 (30)	18 (32,7)	[b]0,660
	Boys	92 (70,8)	34 (75,6)	21 (70)	37 (67,3)	
Family income n (%)	<MMW	20 (15,4)	8 (17,8)	4 (13,3)	8 (14,5)	[b]0,904
	MMW	73 (56,2)	24 (53,3)	19 (63,3)	30 (54,5)	
	>MMW	37 (28,5)	13 (28,9)	7 (23,3)	17 (30,9)	
Mothers' educational level n (%)	No school	12 (9,2)	6 (13,3)	0 (0)	6 (10,9)	[c]0,001**
	Primary school	87 (66,9)	32 (71,1)	14 (46,7)	41 (74,5)	
	Middle school	26 (20,0)	7 (15,6)	12 (40,0)	7 (12,7)	
	University	5 (3,8)	0 (0)	4 (13,3)	1 (1,8)	
Fathers' educational level n(%)	No school	5 (3,8)	2 (4,4)	1 (3,3)	2 (3,6)	[c]0,019*
	Primary school	84 (64,6)	29 (64,4)	18 (60,0)	37 (67,3)	
	Middle school	32 (24,6)	13 (28,9)	4 (13,3)	15 (27,3)	
	University	9 (6,9)	1 (2,2)	7 (23,3)	1 (1,8)	
Family history of SLD n (%)	Absent	76 (58,5)	21 (46,7)	30 (100)	25 (45,5)	[b]0,001**
	Present	54 (41,5)	24 (53,3)	0 (0)	30 (54,5)	
Family history of speech delay n (%)	Absent	83 (63,8)	24 (53,3)	25 (83,3)	34 (61,8)	[b]0,027*
	Present	47 (36,2)	21 (46,7)	5 (16,7)	21 (38,2)	

[a]Student T Test, [b]Pearson Ki Square Test, [c]Fisher Freeman Halton Test, *p<0,05, **p<0,01, MMW=Monthly Minimum Wage

Table 2: Comparison of the groups in terms of speech delay, speech disorder, birth time, intrauterine tobacco smoke exposure

		Total N(%)	SLD Group N(%)	DEHB Group N(%)	Comorbid Group N(%)	p
Speech Delay	Absent	81 (62,3)	25 (55,6)	27 (90)	29 (52,7)	[b]0,002*
	Present	49 (37,7)	20 (44,4)	3 (10.0)	26 (47,3)	
Speech Disorder	Absent	92 (70,8)	26 (57,8)	30 (100)	36 (65,5)	[b]0,001*
	Present	38 (29,2)	19 (42,2)	0 (0)	19 (34,5)	
Birth time	Term	105 (80,8)	35 (77,8)	25 (83,3)	45 (81,8)	[c]0,790
	Pre-term	16 (12,3)	7 (15,6)	4 (13,3)	5 (9,1)	
	Post-term	9 (6,9)	3 (6,7)	1 (3,3)	5 (9,1)	
Intrauterine tobacco smoke exposure	Absent	68 (52,3)	25 (55,6)	14 (46,7)	29 (52,7)	[b]0,749
		62 (47,7)	20 (44,4)	16 (53,3)	26 (47,3)	

[b]Pearson Ki Square Test, [c]Fisher Freeman Halton test, *p<0,01

Table 3: Comparison of the groups in terms of behavioral indicators of brain laterality

		Total N(%)	SLD Group N(%)	DEHB Group N(%)	Comorbid Group N(%)	p
Handedness	Right	107 (82,3)	33 (73,3)	30 (100)	44 (80)	[b]0,010*
	Left	23 (17,7)	12 (26,7)	0 (0)	11 (20)	
Eyedness	Right	83 (63,8)	26 (57,8)	26 (86,7)	31 (56,4)	[b]0,012*
	Left	47 (36,2)	19 (42,2)	4 (13,3)	24 (43,6)	
Footedness	Right	109 (83,8)	35 (77,8)	30 (100)	44 (80)	[b]0,022*
	Left	21 (16,2)	10 (22,2)	0 (0)	11 (20)	
Crossed laterality	Absent	89 (68,5)	30 (66,7)	26 (86,7)	33 (60)	[b]0,039*
	Present	41 (31,5)	15 (33,3)	4 (13,3)	22 (40)	

bPearson Ki Square Test, *p<0,05

DISCUSSION

We demonstrated that left-footedness and left eyedness were associated with Speech Disorders in patients with SLD and/or ADHD. Besides, left side preferences and crossed laterality were common among SLD (with/without ADHD) but not in pure ADHD patients. Our hypotheses related to brain laterality in ADHD were rejected. Since it is the first study to evaluate behavioral markers of brain laterality in ADHD and SLD by controlling other environmental factors that may affect brain laterality, and considering its relationship with speech difficulties, we think that its results will contribute to the literature.

Learning is a complex and dynamic process based on both perceptive and motor acts. Researchers state that laterality is paramount to the development of academic achievement. Learning difficulties can be a consequence of laterality disruption and disturbances on spatial organization [15]. In their study Scerri et al., (2011) have found that in SLD patients, greater relative right-hand skill is associated with minor allele of single nucleotide polymorphism, which is an intron of PCSK6, a gene that encodes a protein involved in left-right axis determination [8]. Increased rates of left handedness in dyslexia have been demonstrated [16]. In their study, Siviero et al (2002) have shown that increased left handedness (15,4 % vs 0%), but not left eyedness (30,8% vs 26,7%), is more common in dyslexia than normal controls [13]. Another finding of laterality in SLD patients is the increased crossed-laterality rates (as high as 46,4%) [13] which has been shown to be associated with academic achievement or intelligence [15]. These finding indicates that cerebral asymmetry and dyslexia are linked with each other.

This study demonstrated the presence of abnormal brain laterality in SLD patients (with or without comorbid ADHD) compared to healthy controls and ADHD patients. Because we excluded any environmental risk factors affecting the development of laterality, our findings support the studies that has demonstrated the association of left-handedness and crossed laterality with SLD itself.

Human language is a complex communication system processed by specialized brain systems localized in the left cerebral hemisphere in the majority of people. It has been proposed that handedness emerged as a consequence of the evolution of language [8]. In patients with specific language impairment, significant lack of left lateralization in all core language regions (inferior frontal gyrus-opercularis, inferior frontal gyrus-triangularis, supramarginal gyrus and superior temporal gyrus), across single or combined task analysis [17] and hypoactivation at rest affecting the right parietal region and a right hyperactivation with lower left asymmetry involving the temporal lobes [18], have been reported in fMRI studies. In this study, we found that speech problems were common among SLD patients, and in these SLD patients, whether they had comorbid ADHD or not, left eyedness and left footedness were associated with SD but not with speech delay. Dyslexia and specific language impairment are common childhood disorders that show considerable co-morbidity and diagnostic overlaps and have been suggested to share some genetic etiology [19]. In this context, our finding related to speech problems and laterality suggests that the main determinant of brain laterality is the speech development in patients with SLD.

In ADHD samples right hemisphere dysfunction is demonstrated in many studies. Simoes et al. (2017) state that atypical brain laterality together with right hemisphere dysfunction are among the main components of ADHD [7]. Decreased brain laterality has been shown to be associated with inattention [20] and total ADHD symptom [21] scores. Consistently, compared to right handed students, left handed ones have a higher probability of suffering from ADHD [7]. Studies demonstrate that in ADHD patients, non-right handedness [7,22] and crossed laterality (79-41% in ADHD and control groups, respectively) are more common and cross laterality is associated with behavioral problems [23]. On the contrary, there are studies showing that in ADHD handedness is not different [24] and not associated with symptom scores or comorbidity [25]. Besides, Tran and Voracek (2018) found that footedness, not the handedness, correlated with symptomatology in ADHD [24].

Our findings demonstrated that left side preferences and cross laterality were not high

among pure ADHD cases and even statistically significantly lower in these patients, compared to SLD patients. Besides the strong genetic influences, early life environmental stressors (pre-peri and postnatal) and learning processes play role in handedness [12]. Many other psychiatric disorders (including SLD, autism, schizophrenia, anxiety disorder), medical diseases (such as epilepsy, autoimmune diseases, hearing and vision impairments) and birth complications have been reported to affect lateralization of the brain function [5,12,13,14]. Based on this knowledge in order to assess the relationship between a specific neurodevelopmental disorder and brain laterality, other factors should be controlled and excluded. However, it is not clear whether the environmental factors affecting brain laterality were controlled in the previous studies. Because all these factors were controlled and excluded in this study sample, we think that our study shows the laterality ratios in ADHD more accurately than previous studies.

Potential limitations of our study include the relatively small sample size, the lack of a healthy controls and the absence of assessment of ambiguous laterality in the patients. Moreover, assessment of ear preference by audiometric measurements will be helpful in determining brain laterality.

CONCLUSIONS

Results of this study showed that left side preference was associated with speech disorders in ADHD and SLD patients, and many SLD patients, but not ADHD patients, had left side preference and crossed laterality, as well as speech difficulties. These findings suggest that speech may a mediating role in development of behavioral indicators of laterality. Studies with larger sample size and with healthy controls will be useful to further examination of the relationship between speech problems, SLD and brain laterality.

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The Importance of the De Ritis Ratio and Glasgow Prognostic Score in prehypertensive patients

Prehipertansif Hastalarda De Ritis Oranı ve Glasgow Prognostik Skorunun Önemi

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ABSTRACT

Aim: To evaluate Glasgow prognostic score (GPS) and De Ritis ratio in optimal blood pressure and prehypertensive patients, and investigate whether these parameters can predict antihypertensive treatment in the follow-up period.
Methods: A total of 402 patients who were followed up with a 24-hour ambulatory blood pressure with a pre-diagnosis of hypertension between January 2018 and December 2018 were included in the study. Routine laboratory parameters of the patients were recorded in the hospital digital system. The common health system data of the patients was analyzed until June 2020, and those who were started on antihypertensive treatment were recorded.
Results: 402 patients (mean age 40.16 ± 13.01 years, 49% male) were included in the study. 226 of these were in prehypertension group. The mean GPS and the De Ritis ratio, aspartate aminotransferase levels, mean systolic and diastolic blood pressures were different between the groups (p=0.035, p=0.023, p=0.039, p<0.001 and p=0.012, respectively). When patients whose antihypertensive treatment was started and those who did not receive antihypertensive treatment were compared; age, De Ritis ratio and mean diastolic blood pressure differed between the two subgroups (p<0.001, p=0.015 and p=0.040, respectively). Multivariate logistic regression analysis showed that De Ritis ratio and age were, independently, predictors for antihypertensive treatment (OR:3.064, p=0.015 and OR:1.050, p= 0.001 respectively). In ROC curve analysis, both age and De Ritis ratio were successful at predicting the initiation of antihypertensive treatment with an AUC:0.697 and p<0.001 and AUC:0.630 and p=0.018 respectively.
Conclusions: Both GPS and the De Ritis ratio were found to be significantly higher in prehypertensive patients than those with optimal blood pressure. Moreover, the De Ritis ratio, an easily calculated laboratory parameter, can be used as a predictive value for antihypertensive treatment.

Keywords: De Ritis ratio, Glasgow prognostic score, prehypertension

ÖZ

Amaç: Optimal kan basıncı ve prehipertansif hastalarda Glasgow prognostik skoru (GPS) ve De ritis (AST/ALT) oranını değerlendirmek ve bu parametrelerin takip döneminde antihipertansif tedaviyi tahmin edip edemeyeceğini araştırmayı amaçladık.
Yöntemler: Ocak 2018-Aralık 2018 tarihleri arasında kliniğimizde hipertansiyon ön tanısıyla 24 saat ambulatuvar kan basıncı monitörizasyonu ile izlenen toplam 402 hasta çalışmaya dahil edildi. Hastaların rutin laboratuvar parametreleri hastane dijital sisteminden kaydedildi. Hastaların medikasyon verileri ulusal sağlık sisteminden Haziran 2020'ye kadar analiz edilerek antihipertansif tedavi başlanan hastalar kayıt altına alındı.
Bulgular: Çalışmaya 402 hasta (ortalama yaş 40.16 ± 13.01 yıl) dahil edildi (% 49 erkek). Bunların 226'sı prehipertansiyon grubundaydı. Prehipertansiyon grubunda ortalama GPS ve De Ritis oranı, aspartat aminotransferaz seviyeleri, ortalama sistolik ve diyastolik kan basınçları daha yüksek ve istatistiksel olarak anlamlı belirlendi (sırasıyla p = 0,035, p = 0,023, p = 0,039, p = <0,001 ve p = 0,012). Antihipertansif tedavi başlanan ile başlanmayan hastalar karşılaştırıldığında; yaş, De Ritis oranı ve ortalama diyastolik kan basıncı antihipertansif tedavi alan grupta daha yüksek belirlendi (sırasıyla p <0,001, p = 0,015 ve p = 0,040). Çok değişkenli lojistik regresyon analizinde De Ritis oranı ve yaş antihipertansif tedavi başlanması için bağımsız öngördücüler oldukları saptandı (sırasıyla OR: 3.064, p = 0.015 ve OR: 1.050, p = 0.001). ROC eğrisi analizinde, hem yaş hem de De Ritis oranı sırasıyla EAA: 0.697 ve p <0.001 ve EAA: 0.630 ve p = 0.018 ile antihipertansif tedavinin başlamasını öngörmede başarılıydı.
Sonuçlar: Hem GPS hem de De Ritis oranı prehipertansif hastalarda optimal kan basıncına sahip olanlara göre anlamlı olarak daha yüksek bulundu. Ayrıca kolay hesaplanan bir laboratuvar parametresi olan De Ritis oranı, antihipertansif tedavi başlanması için bir tahmin değeri olarak kullanılabilir.

Anahtar Kelimeler: De ritis oranı, Glasgow prognostik skoru, prehipertansiyon

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INTRODUCTION

Hypertension (HT) is the leading component of global disease burden and acts as a major cause of cardiovascular (CV) diseases; a higher mortality in hypertensive population is well known in many countries through national level studies [1].

Pre-HT was defined as a systolic blood pressure (SBP) between 120–139 mmHg or diastolic blood pressure (DBP) between 80–89 mmHg [2]. The definition of HT changed in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines, which caused confusion in the diagnosis and treatment of patients with stage 1 HT, previously referred to as pre-HT [3].

In the presence of pre-HT, the risk of CV events in patients is significantly increased compared to those with normal blood pressure levels. The increase in arterial blood pressure develops over the years, and the diagnosis of pre-HT and HT is mostly made in the 4-5th decades. In patients defined in the pre-HT stage, the development of HT can be prevented by appropriate lifestyle changes and correction of known risk factors for the development of HT. However, although lifestyle changes and risk factors are optimized in some patients, HT develops in patients with progressive increase in blood pressure, and medical treatment is required. The pathophysiology underlying the development of HT is not unique, but more than one factor plays a role. Endothelial dysfunction and chronic inflammation are some of well-determined factors involved in the pathogenesis of HT [4,5]. Tsounis, Huang and Polónia have previously shown that there is a relationship between inflammatory markers / risk scores and endothelial dysfunction in the development of HT [6-8].

It has been determined that the GPS and De Ritis ratio (Glasgow prognostic score and AST/ALT), which is mainly proposed to determine the prognosis of malignancies, is an indicator of cardiac mortality and morbidity in later periods. In patients in the pre-HT stage, simple laboratory parameters or scores that will predict HT progression, will be of great importance in daily life.

Since both laboratory parameters can determine inflammation and endothelial dysfunction, they may be markers for the progression of HT in prehypertensive patients [9-13]. In this study, we planned to investigate whether these two parameters differ in optimal BP and prehypertensive patients and whether De Ritis and GPS values in prehypertensive patients, at the time of the diagnosis of pre-HT, can help in the initiation of medical treatment in the follow-up.

METHODS

Four hundred and two patients who were followed for 24-hour ambulatory blood pressure monitoring (ABPM) with pre-diagnosis of HT in our clinic, between January and December 2018, were included in this retrospective study. The study flow diagram is presented in Figure 1.

The demographic and medical characteristics of the patients were obtained from patients' files and the digital system. Optimal blood pressure was defined as a systolic blood pressure (SBP) <120 mm Hg and, diastolic blood pressure (DBP) <80 mm Hg and pre-HT was defined as SBP 120-129 mm Hg and DBP<80 mm Hg and HT as ≥ 130/80 mm Hg[2]. Patients with known inflammatory disease, chronic liver disease, malignancy, those who were under 18 and over 85 years of age, those with coronary artery disease, diabetes mellitus, those who had any treatment that might increase liver function tests like statins and patients using medicines that lower arterial blood pressure for any reason, missing or insufficient ambulatory blood pressure patients and with missing laboratory parameters, were all excluded from the study.

Follow-up data of the patients until June 2020 were obtained from hospital record and phone interviews. The data of 278 were recorded during their check-up and the remaining 124 were reached by telephone. Those who started antihypertensive treatment due to high levels of arterial blood pressure during their follow-up were noted.

All blood samples were collected and the laboratory measurements of serum values of albumin, C-reactive protein (CRP), liver and kidney function tests, lipid parameters, other biochemical tests and complete blood count values were studied

in venous blood samples, taken at admittance. The De Ritis ratio was calculated as aspartate aminotransferase/ alanine aminotransferase (AST / ALT) and the GPS was defined based on the presence of hypoalbuminemia (<35 g/L) and elevated CRP (>10 mg/L): if both were abnormal, the score was 2; if either was abnormal, the score was 1; if neither was abnormal, the score was 0.

Statistical analysis: The Levene 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 Kruskal-Wallis was used for variables without normal distribution. Categorical variables were presented as total number and percentages, and compared using the chi-square test. Correlations between variables was accomplished with the Pearson correlation if the variables distributed homogenously, and the Spearmen correlation if not. Multivariate analysis using logistic regression models tested variables with p ≤ 0.25 in univariate analysis. Receiver operating characteristics (ROC) curve analysis was performed to demonstrate the predictive values of the variables and the area under curve (AUC) of the scores were compared using the Delong method. A two-tailed p value of <0.05 was considered as statistically significant and 95% confidence interval (95 % CI) were presented for all odds ratios. All statistical analyses were performed using the SPSS Windows software (ver.15.0; IBM, NY, USA).

RESULTS

A total of 402 patients (mean age, 40.16 ± 13.01 years; 197 men [49%]) were included in this retrospective cohort study. Of these patients 226 were in prehypertension group with a mean SBP / DBP of 124.92 ± 2.52 / 73.20 ± 5.24 mm Hg and the remaining in optimal blood pressure group with 112.93 ± 4.55 / 68.63 ± 4.69 mm Hg (p<0.001 and p= 0.012, respectively).

There were no participants with GPS 3 in the study. Out of 176 individuals in the optimal blood pressure group, 163 (92.6%) of them had GPS 0 while this number was 202 (89.3%) in the prehypertension group. Table 1 shows the baseline demographic and laboratory results of the groups. The patients in pre-HT group were followed between January 2018 and June 2020 and antihypertensive treatment was initiated for 36 of them during their follow-up. Of these patients 14 (38.9) were male and the mean age was 47.22 ± 11.38. When the subgroups, according to initiation of antihypertensive treatment, were analyzed, they differed only in terms of age, De Ritis ratio and DBP levels, with p<0.001, 0.015 and 0.040, respectively (Table 2).

Table 1: Baseline characteristics and laboratory results of groups and statistical analysis

	Prehypertension group(n=226)	Control group (n=176)	p
	mean ± sd	mean ± sd	
	39.85 ± 13.71	40.56 ± 12.07	0.589
Gender, m (%)	108 (47.7)	89 (50.5)	0.580
Systolic BP, mm Hg	124.92 ± 2.52	112.93 ± 4.55	<0.001*
Diastolic BP, mm Hg	73.20 ± 5.24	68.63 ± 4.69	0.012*
Glucose, mg/dL	97.28 ± 20.46	98.72 ± 24.02	0.375
Urea, mg/dL	25.71 ± 8.03	25.27 ± 8.06	0.644
Uric acid, mg/dL	5.50 ± 1.68	4.73 ± 1.94	0.004*
Creatinine, mg/dL	0.67 ± 0.16	0.64 ± 0.14	0.066
Na, mEq/L	146.89 ± 98.67	138.12 ± 11.58	0.311
K, mEq/L	4.42 ± 0.60	4.36 ± 0.58	0.328
AST, U/L	23.51 ± 7.70	21.81 ± 7.44	0.039*
ALT, U/L	23.66 ± 12.89	21.29 ± 10.18	0.068
LDL, mg/dL	141.67 ± 43.69	145.38 ± 35.28	0.505
HDL, mg/dL	48.52 ± 10.68	49.96 ± 13.72	0.394
Triglycerides, mg/dL	174.11± 110.41	174.08 ± 113.11	0.998
Albumin, mg/dL	42.81 ± 5.20	43.21 ± 4.13	0.672
CRP, mg/dL	6.42 ± 4.31	6.09 ± 4.77	0.232
WBC count, 103 /mL	7.77 ± 2.20	9.75 ± 15.24	0.077
Hgb, g/dL	13.65 ± 1.87	13.45 ± 1.66	0.224
Plt count, 103/mL	266.32 ± 68.34	271.64±73.60	0.498
GPS	0.10 ± 0.30	0.04 ± 0.20	0.035*
De Ritis ratio	1.28 ± 0.43	1.16 ± 0.36	0.023*

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BP: blood pressure, CRP: C-reactive protein, GPS: Glasgow prognostic score, HDL: high density lipoprotein cholesterol, Hgb: hemoglobin, K: potassium, LDL: low density lipoprotein cholesterol, Na: sodium, WBC: white blood cell, Plt : platelet

Multivariate logistic regression analysis showed that age and De Ritis ratio were independently predictors of initiation of antihypertensive treatment (Table 3). In ROC curve analysis, both age and De Ritis ratio were successful at predicting the initiation of antihypertensive treatment with an AUC:0.697 and p<0.001 and AUC:0.630 and p=0.018 respectively (Figure 2).

Table 2: Characteristics of prehypertension group

	No treatment group (n=190)	Antihypertensive drug group (n=36)	p
Gender, m(%)	94(49.4)	14(38.8)	0.244
Glucose, mg/dL	100 ± 27	101 ± 21	0.803
Age, years	38.45 ± 13.69	47.22 ± 11.38	<0.001*
Urea, mg/dL	25.5 ± 8	26.3 ± 8	0.635
Creatinine, mg/dL	0.67 ± 0.16	0.65 ± 0.13	0.449
Uric acid, mg/dL	5.42 ± 1.71	5.84 ± 1.52	0.324
AST, U/L	23.46 ± 7.76	23.77 ± 7.51	0.842
ALT, U/L	23.92 ± 3.28	22.33 ± 10.72	0.531
Na, mEq/L	139 ± 2,2	139 ± 1.4	0.855
K, mEq/L	4.40 ± 0.43	4.56 ± 1.10	0.192
CRP, mg/dL	6.46 ± 3.94	6.21 ± 3.89	0.988
Triglycerids, mg/dL	167.98 ± 104.93	205.64 ± 133.51	0.144
LDL-C, mg/dL	140 ± 45	148 ± 32	0.467
HDL-C, mg/dL	47.75 ± 8.95	52.34 ± 16.69	0.079
Systolic BP, mm Hg	125.01 ± 2.70	124.47 ± 1.72	0.747
Diastolic BP, mm Hg	72.09 ± 5.03	78.76 ± 0.90	0.040*
GPS	0.10 ± 0.30	0.085 ± 0.28	0.727
De Ritis ratio	1.25 ± 0.41	1.45 ± 0.46	0.015*

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BP: blood pressure, GPS: Glasgow prognostic score, HDL-C: high density lipoprotein cholesterol, K: potassium, LDL-C: low density lipoprotein cholesterol

Table 3: Univariate and Multivariate logistic regression of variables for antihypertensive treatment

	Univariate analysis			Multivariate analysis		
	OR	95 %CI	P	OR	95 % CI	p
Age	1.047	1.020-1.076	0.001	1.050	1.021-1.080	0.001
Gender, male	1.539	0.743-3.186	0.256			
DBP	1.053	0.975-1.138	0.186	1.062	0.976-1.156	0.165
SBP	0.913	0.545-1.529	0.729			
De Ritis Ratio	2.699	1.169-6.230	0.020	3.064	1.238-7.586	0.015
LDL	1.004	0.993-1.014	0.466			
GPS	0.797	0.224-2.840	0.726			
Na	1.018	0.841-1.232	0.854			
K	1.420	0.804-2.508	0.262			

DBP: diastolic blood pressure, SBP: systolic blood pressure, OR: Odds Ratio, CI: confidence interval, Na: Sodium, K: potassium, GPS: Glasgow prognostic score, LDL-C: low density lipoprotein cholesterol

DISCUSSION

This study showed that 1) in the 24-hour ambulatory blood pressure follow-up, 31.3% of the patients had pre-HT, 2) the mean systolic-diastolic blood pressure, mean GPS and De Ritis rate were higher in patients with pre-HT. 3) It was determined that pre-HT patients who started antihypertensive treatment were older, the rate of De Ritis ratio and mean diastolic blood pressure were higher, 4) Multivariate logistic regression analysis showed that De Ritis rate and age were independent predictors for initiation of antihypertensive therapy. These results are, to our knowledge, the first study in the literature to show the relationship between Pre-HT and De Ritis ratio and GPS.

Progression of pre-HT, which is determined according to the JNC 7 criteria and based on office blood pressure values, to HT is a frequently encountered health and social problem. Although there is no consensus on the necessity of treatment of pre-HT and the factors that cause it to progress to HT, many studies have expressed opinions on these issues [14]. In a large-scale study, PREVER-prevention, low dose chlortalidone and amiloride reduces the risk of HT and affects left ventricular mass in patients with pre-HT beneficially [15]. Furthermore, Lüders et al. found that angiotensin converting enzyme inhibitors reduced the risk of progression to manifest HT in patients with high-normal office blood pressure [16].

Multiple factors such as age, gender, increased BMI, high basal systolic/diastolic blood pressure and hyperuricemia, were evaluated in patients diagnosed with pre-HT, and there are studies showing that these increase the risk of developing HT [17]. The fact that hyperuricemia is a factor that increases both the risk of pre-HT and the progression to HT, has been supported by the studies of Liu and Kuwabara et al [18,19]. In our study, serum uric acid levels were higher in pre-HT group similar to these studies but we did not find any significant difference when the ones who received a antihypertensive treatment and who did not were compared.

Some studies indicate that the female gender increases the risk of developing HT whereas some indicate it's the male gender [20]. In our study,

we did not find any risk increase depending on gender. As the prevalence of HT increases with increasing age, the risk of progression of pre-HT to HT also increases, and this fact was also demonstrated in our study. Although there was no difference in age between patients with pre-HT and optimal blood pressure, the mean age of those diagnosed with HT and started on treatment in the pre-HT group was found to be significantly higher than the others. High basal systolic and diastolic blood pressure also affects the development of HT [21]. In our study, we were able to find that the group in need of antihypertensives only had higher diastolic blood pressure values, compared to the others.

Pre-HT patients are at risk of morbidity and mortality due to cardiovascular and cerebrovascular events because of endothelial dysfunction [22]. There is yet no scoring system or laboratory parameter that determines whose treatment should be started. The GPS and the De Ritis ratio are measurements that are used as indicators of endothelial dysfunction and consist of simple calculable laboratory parameters. In our study, which we planned based on this hypothesis, we found that the GPS and the De Ritis ratio in pre-HT patients were significantly higher than those with optimal blood pressure. In addition, it was observed that the De Ritis ratio in patients who progressed to HT was statistically significantly higher, than those who remained in the pre-HT period. The difference in GPS values was not observed in these subgroups. Moreover, the De Ritis ratio was successful in predicting the initiation of antihypertensive drugs in our study.

Our study had more than one limitation. The most important of these is that it was a small group of patients and it was single-centered. Groups were determined according to the mean values of ambulatory blood pressure monitoring, so the number of participants was low. If the office blood pressure levels were based on, the predictive power of starting antihypertensive treatment of variables may be changed. Furthermore, the design of the protocol was retrospective.

CONCLUSIONS

GPS and the De Ritis ratio were higher in prehypertensive patients than the ones with optimal blood pressure levels. Furthermore, the De Ritis ratio was found significantly higher in patients who were started on antihypertensive treatment, compared to those who did not use antihypertensives and it was also an independent predictor of initiation of treatment. However, there is a need for prospective studies with large participation, multi-center and long follow-up, for its use as a parameter that can predict the initiation of antihypertensive therapy.

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RESEARCH ARTICLE

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Investigation of Systemic Immune Inflammatory Index and Prognostic Nutritional Index in Prediction of Major Adverse Cardiovascular and Cerebral Events Occurring After Coronary Artery Bypass Operations

Koroner Arter Bypass Operasyonları Sonrasında Ortaya Çıkan Major Advers Kardiyovasküler Ve Serebral Olayları Öngörmede Sistemik Immun Inflamatuar Indeks Ve Prognostik Nutrisyonel Indeksin Yerlerinin Araştırılması

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ABSTRACT

Aim: The most valuable treatment method for coronary artery disease is coronary artery bypass graft (CABG) surgery. Major cardiovascular and cerebral events (MACCE) are important challenges, and it is particularly important to reveal possible risk factors in this regard. In this study, we aimed to investigate the predictive areas of the prognostic nutritional index (PNI) and the systemic immune inflammation index (SII) on early postoperatively developing MACCE, in patients who underwent isolated CABG operation.

Methods: The patients between the ages of 20 and 85 years who underwent consecutive isolated CABG operation in our clinic between May 15th, 2016, and May 15th, 2020, were included in the study retrospectively. In the postoperative period (within a month), those who did not develop MACCE were recorded as Group 1, and those who developed MACCE as Group 2.

Results: A total of 297 consecutive patients were included in the study. Group 1 had 263 patients with a median age of 63 (32-80), Group 2 had 34 patients with a median age of 70 (36-85) (P=0.008). There was no difference between the groups in terms of gender, history of cerebrovascular events, smoking, body mass index, hyperlipidemia, ejection fraction, and chronic obstructive pulmonary disease rates. As a result of multivariate analysis, advanced age (OR: 1.230 CI 95%: 1.050-1.319 P=0.024), NLR (OR: 1.974 CI 95%: 1.614-3.120, P=0.009), SII (OR: 3.880, CI 95%: 2.690-6.150, P<0.001) and PNI (OR: 2.424, CI 95%: 1.880-3.880, P=0.002) values were determined as independent predictors for predicting early postoperative MACCE.

Conclusions: With this study we revealed that SII and PNI values, which are among the inflammatory parameters and which can be obtained cheaply and easily, may be good predictors for MACCE emerging after CABG operations.

Keywords: Coronary artery bypass grafting, Inflammation, Nutritional index, Postoperative complication

ÖZ

Amaç: Koroner arter hastalığı için en değerli tedavi yöntemi koroner arter baypas greft (KABG) ameliyatıdır. Başlıca kardiyovasküler ve serebral olaylar (MACCE) önemli sorunlardır ve bu konuda olası risk faktörlerini ortaya çıkarmak çok önemlidir. Bu çalışmada, izole KABG operasyonu geçiren hastalarda erken postoperatif gelişen MACCE üzerine prognostik nutrisyonel indeks (PNI) ve sistemik immün inflamasyon indeks (SII)'in prediktif yerlerini araştırmayı amaçladık.

Yöntemler: Kliniğimizde 15.05.2016-15.05.2020 tarihleri arasında ardışık izole KABG operasyonu geçiren 20-85 yaşları arasındaki hastalar retrospektif olarak çalışmaya dahil edildi. Postoperatif dönemde (bir ay içinde) MACCE gelişmeyenler Grup 1, MACCE gelişenler Grup 2 olarak kaydedildi.

Bulgular: Çalışmaya toplam 297 ardışık hasta dahil edildi. Grup 1'de medyan yaşı 63 (32-80) olan 263 hasta, Grup 2'de medyan yaşı 70 (36-85) olan 34 hasta vardı (P = 0.008). Gruplar arasında cinsiyet, serebrovasküler olay öyküsü, sigara kullanımı, vücut kitle indeksi, hiperlipidemi, ejeksiyon fraksiyonu ve kronik obstrüktif akciğer hastalığı oranları açısından fark yoktu. Çok değişkenli analizin sonucunda ileri yaş (OR: 1.230 CI 95%: 1.050-1.319 P=0.024), NLR (OR: 1.974 CI 95%: 1.614-3.120, P=0.009), SII (OR: 3.880, CI 95%: 2.690-6.150, P<0.001) and PNI (OR: 2.424, CI 95%: 1.880-3.880, P=0.002) değerleri erken postoperatif MACCE'yi öngörmede bağımsız prediktörler olarak tespit edildi.

Sonuçlar: Bu çalışma ile, ucuz ve kolay elde edilebilen inflamatuar parametreler arasında yer alan SII ve PNI değerlerinin, KABG operasyonlarından sonra ortaya çıkan MACCE için iyi prediktörler olabileceğini ortaya koyduk.

Anahtar Kelimeler: Koroner arter baypas greft, İnflamasyon, Nutrisyonel indeks, Postoperatif komplikasyon

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INTRODUCTION

Coronary artery disease (CAD) is one of the important causes of mortality and morbidity today. The most effective treatment method for this disease is coronary artery bypass graft (CABG) surgery. These operations are mostly performed with cardiopulmonary bypass (CPB) [1,2]. Sudden death, postoperative myocardial infarction, cerebrovascular event and decompensated heart failure states that occur after these procedures are known as major postoperative cardiovascular and cerebral events (MACCE). The neutrophil-lymphocyte ratio (NLR), one of the simply obtainable inflammatory parameters with proven efficacy, has been shown as a predictor for MACCE emerging after coronary bypass operations [3]. In addition, it has been shown that other easily obtainable blood parameters such as the platelet lymphocyte ratio (PLR), may also be predictors of mortality and adverse outcomes in cardiovascular surgery [4]. The systemic immune inflammation index (SII), PLR and NLR, values obtained from these blood parameters which have been the subject of many studies, have been used as a prognostic inflammatory marker in various fields of medicine [5-7]. In a recent study, it has been revealed a predictive factor for adverse events after off-pump CABG operations [8].

The prognostic nutritional index (PNI), which can be obtained from routine blood parameters, is a factor that shows the nutritional status and has prognostic significance. PNI value is calculated with a formula that includes albumin value and lymphocyte counts [9]. One particular study showed that PNI value might be associated with morbid results after CABG surgeries [10].

In this current study, the aim was to investigate the predictive places of PNI and SII values on early postoperatively developing MACCE, in patients who underwent isolated CABG operation with CPB.

PATIENTS AND METHODS

The patients between the ages of 20 and 85 years who underwent consecutive isolated CABG operations with cardiopulmonary bypass in our clinic between May 15th, 2016 and May 15th, 2020 were included in the study retrospectively. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices and approval of the local ethics committee was duly obtained (HRU/20.14.04 Date: August 17th, 2020). The patients who underwent urgent coronary bypass, the patients scheduled for additional cardiac surgery such as valve and aneurysm, reoperations, those with permanent stroke, those with systemic inflammatory diseases, those with chronic autoimmune disease, the patients with chronic renal failure (Preop creatinine value>2mg/dL), the ones whose left ventricular ejection fraction was 30 and below and those with hematological diseases, were all excluded from the study. As a result of the exclusion criteria, 297 consecutive patients were included in the study. Demographic characteristics of the patients (age, gender, history of systemic diseases such as diabetes mellitus and hypertension, etc.), ejection fractions, preoperative blood parameters (hemogram [White blood cell (WBC)], neutrophil, lymphocyte, NLR, PLR, SII), biochemistry (Creatinine), urea, albumin, C-reactive protein (CRP) were recorded. Pump durations, stay durations during hospitalization and intensive care unit, drainage amounts, used blood product amounts were recorded operatively and postoperatively. In the postoperative period (within a month), those who did not develop MACCE were recorded as Group 1, and those who developed MACCE as Group 2.

Calculation of Parameters

Preoperative blood parameters of all patients were obtained from blood samples taken from their peripheral venous structures during their admission to our clinic. The sample was collected in tubes containing ethylenediaminetetraacetic acid and was used for automatic blood count with the usual hospital procedures. An automated hematological analyzer was used for measuring hematological parameters (Coulter LH 780 Analyzer, CA, USA). Index values were obtained by using the following formulas from the data in these parameters.

PNI=Albumin (g/L) + Lymphocyte (10 3/μL) x 5

SII=Platelet count (10 3/μL) x Neutrophil (10 3/μL)/Lymphocyte (10 3/μL)

Identification of Major Adverse and Cerebrovascular Events

Postoperative mortality, death occurred within 1 month due to all causes, Postoperative myocardial infarction development, defined as having increased biomarker values (creatine kinase-MB or cardiac troponin levels) by at least five-fold and Q waves occurring in at least two ECG derivations or occurring of ST segment changes or new left bundle branch block, the need for revascularization, the need for surgery or endovascular revascularization again after the operation, Re-intervention, requiring re-hospitalization due to any cardiovascular cause within one postoperative month, Stroke development, post-operative central neurological deficit that lasts at least 24 hours and Decompensated heart failure, the postoperative need of positive intropic support (>24 hours) or intraaortic balloon pump, were all defined as postoperative MACCE. Patients who developed at least one of these conditions were recorded as Group 2.

Statistical Analysis

In our study, the SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program was used to analyze the data. Means and standard deviations were calculated for mediational, continuous and ordinal data, using descriptive analysis methods. The "Kolmogorov-Smirnov test and Shapiro-Wilk test" were used for normality distribution analysis. While Student's t test was used for the data presenting normal distribution, the Mann-Whitney U test was used for data that did not conform to normal distribution. This data were shown as mean ±sd or as mean (interquartile range). Categorical variables were shown as frequency and percentage, and the "Chi Square test" was used for analysis. Univariate and multivariate binary logistic regression analysis was used to analyze postoperative MACCE predictors. P value's being less than 0.05 was considered statistically significant. In predicting postoperative MACCE, receiver operating characteristics (ROC) curve analysis was performed for NLR, PNI and SII values and the areas under the curve (AUC) were calculated.

RESULTS

A total of 297 patients were included in the study. Group 1 had 263 patients with a median age of 63 (32-80), Group 2 had 34 patients with a median age of 70 (36-85) (P=0.008). There was no difference between the groups in terms of gender, history of cerebrovascular events, smoking, body mass index, hyperlipidemia, ejection fraction and chronic obstructive pulmonary disease (COPD) rates. Former percutaneous coronary intervention, hypertension (HT), diabetes mellitus (DM) rates and EuroSCORE II values were found to be significantly higher in Group 2 (P=0.041,P=0.034, P=0.011, P<0.001, respectively) (Table 1).

Table 1. Demographic datas and preoperative features of the patients

Variables	Group 1 (N= 263)	Group 2 (N= 34)	P value
Age(years) (mean±sd)	63 (32- 80)	70 (36- 85)	0.008‡
Male gender, n(%)	184 (69.9%)	25 (73.5%)	0.745*
Hypertension, n (%)	169 (64.2%)	27 (79.4%)	0.034*
Diabetes mellitus, n (%)	46 (17.5%)	12 (35.3%)	0.011*
Previous PCI, n(%)	65 (24.7%)	13 (38.2%)	0.041*
Current smoker, n (%)	88 (33.4%)	10 (29.4%)	0.678*
COPD, n (%)	28 (10.6%)	7 (20.5%)	0.194*
Previous CVA	12 (4.5%)	4 (11.7%)	0.356*
EuroSCORE II	2.1 (0.5- 6.4)	3 (0.5- 8.9)	<0.001‡
BMI (kg/m2)	29.3(23.5- 38.7)	30.2 (24- 39.6)	0.427*
Hyperlipidemia, n(%)	98 (37.2%)	14 (41.1%)	0.598*
Ejection fraction (%)	50 (38- 67)	45(33- 66)	0.072‡

* Chi-square test, †Student's t test (Data is axpressed as mean±sd), ‡Mann Whitney U test (Data is expressed as median (interquartile range)) BMI: Body mass index, CVA: Cerebrovascular accident COPD: Chronic obstructive pulmonary disease, EuroSCORE II: European System for Cardiac Operative Risk Evaluation II PCI: Percutaneus coronary intervention

Preoperative laboratory values of the patients are provided in Table 2. Both groups were similar in terms of white blood cell (WBC), hematocrit (Htc), neutrophil, platelet (PLT), urea, creatinine, albumin, PLR, C-reactive protein (CRP) and thyroid function test values. In group 2, while NLR and SII values were significantly higher, PNI and lymphocyte values were significantly lower (P <0.001, for all).

The perioperative characteristics of the patients are given in Table 2. There was no difference between the groups in terms of perfusion times, chest tube drainage amounts, the amount of

used blood products and the number of distal anastomosis. Inotropic support need rates, durations of intensive care and total hospitalization were significantly higher in Group 2 (P=0.014, P <0.001, P <0.001, respectively).

Table 2. Preoperative laboratory variables and perioperative features of the patients of the patients

Variables	Group 1 (n=263)	Group 2 (n=34)	P value ‡
White blood Cell (103/µL)	8.4 (4.7- 14.8)	8.7 (5.1- 15.1)	0.216
Hematocrit (%)	42 (33- 52)	39 (32- 50)	0.198
Platelet (103/µL)	251.6 (136-476.5)	260.6 (140-490.7)	0.118
Neutrophil (103/µL)	4.4 (1.9- 9.9)	4.8 (2.6- 10.2)	0.069
Lymphocyte(103/µL)	2 (0.9- 4.2)	1.7 (0.7- 3.3)	<0.001
Creatinine, mg/dL	1 (0.5- 1.9)	0.96 (0.7- 2)	0.229
Urea, mg/dL	16 (14- 34)	18 (12- 40)	0.416
Albumin (g/L)	39.6 (35- 55)	37.5 (33- 52)	0.109
Free T3 (pg/mL)	2.7 (2.2- 4.9)	2.9 (2.3- 5.2)	0.365
Free T4 (ng/dL)	0.9 (0.6- 1.1)	0.8 (0.7-1.3)	0.497
TSH (µIU/L)	1.4 (0.9- 4.4)	1.5 (0.8- 4.6)	0.414
C Reactive protein (mg/dL)	9.4(0.4- 60.3)	9.8 (0.7- 69)	0.112
NLR	2.4 (1- 6.9)	3.2 (1.3- 10)	<0.001
PLR	151.4 (118.6-234.7)	156.9 (122.5-244.6)	0.065
SII	730 (540-2594)	1240 (630-3276)	<0.001
PNI	50 (36-70)	44 (37- 61)	<0.001
Total perfusion time	100 (55- 175)	106 (57- 180)	0.114
Cross-clamp time	72 (33- 88)	75 (35- 90)	0.317
Total chest tube drainage (ml)	500 (350- 1600)	600 (400-1700)	0.156
Inotropic support, n(%)	27 (10.2)	9 (26.4)	0.014
Packed blood products (units)	5 (5- 10)	6 (4- 11)	0.127
Number of distal anastomoses, n	3 (1- 5)	3 (1- 5)	0.714
Total ICU stay (days)	2 (2- 5)	4 (2-18)	<0.001
Total hospital stay (days)	7 (6- 13)	11 (12- 23)	<0.001

‡Mann Whitney U test, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet lymphocyte ratio, SII: Systemic immune inflammation index, PNI: Prognostic nutritional index, T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone

Logistic regression analysis was performed to predict MACCE predictors early occurring after CABG operations done accompanied by cardiopulmonary bypass (Table 3). In univariate analysis advanced age (OR [odds ratio]: 1.394, 95% CI [confidence interval]: 1.090-1.856, P=0.010), hypertension (OR: 0.774, 95% CI: 0.557-0.992, P=0.038), DM (OR: 0.796, 95% CI: 0.589-0.892, P=0.013), EuroSCORE II (OR: 5.228, 95% CI: 3.794-6.445, P <0.001), need for inotropic support (OR: 1.210, 95% CI: 1.114-1.645, P=0.017), low lymphocyte count (OR: 1.478, 95% CI: 1.116-1.898, P< 0.001), NLR (OR: 2.267, 95% CI: 1.912-3.869, P <0.001), high SII (OR: 4.114, 95% CI: 2.794-6.434, P< 0.001), low PNI (OR: 2.914, 95% CI: 1.894-3.365, P <0.001) values were found to be significantly correlated with the development of MACCE. As a result of multivariate analysis, advanced age (OR: 1.230 CI 95%: 1.050-1.319 P=0.024), NLR (OR: 1.974 CI 95%: 1.614-3.120, P=0.009), SII (OR: 3.880, CI 95%: 2.690-6.150, P<0.001) and PNI (OR: 2.424, CI 95%: 1.880-3.880, P=0.002) values were determined as independent predictors for predicting early postoperative MACCE.

In ROC curve analysis, the cut-off value for preoperative NLR was 2.9 (AUC: 0.710, 95% CI: 0.623-0.797 P <0.001, 73.5% sensitivity and 65.6% specificity), cut-off value for SII was 912.4 (AUC: 0.864, 95% CI: 0.789-0.940 P <0.001, 82.6% sensitivity and 73.4% specificity) and cut-off value for PNI was 46.4 (AUC: 0.730, 95% CI: 0.645-0.815, P <0.001, 75.4% sensitivity and 68.6% specificity) (Figure 1 and Figure 2).

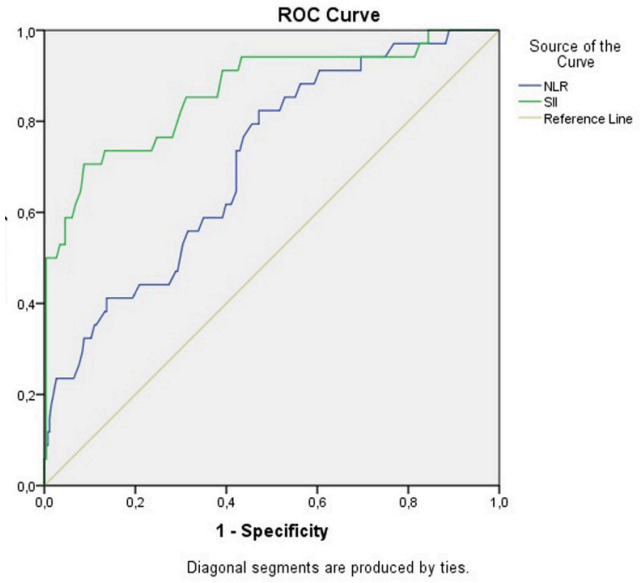

Figure 1: ROC (Receiver operation characteristic) curve and AUC (Area under the curve) for NLR and SII for predicting MACCE. (NLR: cut off: 2.9, AUC: 0.710, 95%CI:0.623- 0.797 P< 0.001, 73.5% sensitivity and 65.6% specificity)(SII: cut-off: 912.4, AUC: 0.864, 95%CI:0.789-0.940 P < 0.001, 82.6% sensitivity and 73.4% specificity)

Table 3. Binary logistic regression analysis to identify factors affecting development of major adverse cardiac and cerebrovascular events

	Univariate analysis			Multivariate analysis		
Variables	P	Exp(B) Odds Ratio	95%C.I. Lower Upper	P	Exp(B)Odds Ratio	95% C.I. Lower Upper
Age	0.010	1.394	1.090- 1.856	0.024	1.230	1.050- 1.319
Hypertension	0.038	0.774	0.557- 0.992	0.198	0.712	0.664- 1.110
Diabetes Mellitus	0.013	0.796	0.589- 0.892	0.170	0.610	0.512- 1.210
EuroSCORE II	<0.001	5.228	3.794- 6.445	--	--	--
Total perfusion time	0.158	1.312	0.945- 1.756	--	--	--
Inotropic support	0.017	1.210	1.114- 1.645	0.218	0.850	0.790- 1.312
Blood product use (units)	0.134	1.080	0.879- 1.114	--	--	--
Lymphocyte(103/µL)	<0.001	1.478	1.116- 1.898	--	--	--
NLR	<0.001	2.267	1.912- 3.869	0.009	1.974	1.614- 3.120
PLR	0.070	1.009	0.792- 1.234	--	--	--
SII	<0.001	4.114	2.794- 6.434	<0.001	3.880	2.690- 6.150
PNI	<0.001	2.914	1.894- 3.365	0.002	2.424	1.880- 3.880

All numerical data included as continuous variable. The goodness of fit of the multivariate model was confirmed by a P-value of 0.734 in the Hosmer-Lemeshow test. EuroSCORE II: European System for Cardiac Operative Risk Evaluation II, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet lymphocyte ratio, SII: Systemic immune inflammation index, PNI: Prognostic nutritional index

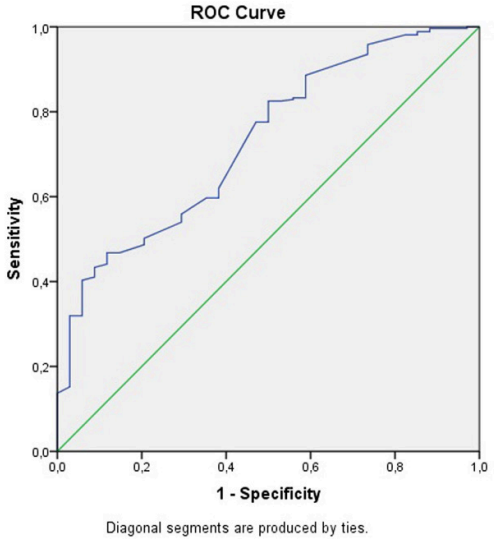

Figure 2: ROC (Receiver operation characteristic) curve and AUC (Area under the curve) for PNI for predicting MACCE (Cut off: 46.4, AUC: 0.730, 95%CI:0.645- 0.815, P< 0.001, 75.4% sensitivity and 68.6% specificity)

DISCUSSION

Coronary bypass surgery is the most effective method for atherosclerotic heart disease, and it can be performed successfully in many clinics today. EuroSCORE II has been largely accepted and is widely used to predict mortality in cardiac surgery. However, several concerns were raised, the score showing poor calibration in some patient groups in whom it underestimated the risk [11]. Also in a study, a simple inflamatuar marker was revealed as a risk factor for the development of MACCE, independent of EuroSCORE [3]. In this sense, in recent years, inflammatory parameters have been widely researched in predicting the prognosis of cardiovascular diseases [3- 5]. In this current study, NLR, SII and PNI values were determined as independent predictors for MACCE, which can be seen in the postoperative period, as well as known risk factors such as age.

Inflammation plays an important role in the pathogenesis and progression of cardiovascular diseases as well as in many diseases. Although many parameters can be used in clinical practice, neutrophils, lymphocytes, thrombocytes and calculations made related to these parameters have been the subject of many clinical studies [12, 13]. Thrombocytes are important inflammatory parameters that mediate the release of cytokines and chemokines, which have important effects on vascular wall inflammation and shear stress formation. In the case of severe chronic inflammation, megakaryocyte proliferation is triggered, and thrombocytosis occurs [14]. Neutrophils, on the other hand, attach to the damaged areas in the vascular bed and cause the relevant chemokines to come to the region, thus atherosclerosis progresses [15]. However, the cellular immune system is mainly responsible for the inflammatory response that occurs after cardiac surgery. This cellular immune system

is activated by lymphocytes, thus increasing neutrophil numbers [16].

In light of this information, NLR and PLR values, which have been the subject of many clinical studies, appear as important prognostic markers. In a study conducted in the field of congenital heart surgery, it has been shown that the preoperative NLR value can be a predictor for low cardiac output syndrome that may occur in the postoperative period [17]. In another cohort study, the predictive role of NLR rate for mortal and morbid outcomes in coronary intensive care units was investigated. At the end of this study, it was shown that the high NLR value could be a predictor for 30-day mortality in these patients as well as renal and respiratory problems in intensive care unit [18].

In the study in which 751 patients were included, who underwent CABG operations, conducted by Gürbüz et al., the patients were followed for an average of 7.8 years and the effect of NLR value on MACCE development was investigated. In this study, the NLR cut-off value for MACCE prediction was found to be 4.32, and the NLR elevation was revealed as a risk factor for the development of MACCE independent of EuroSCORE [3]. In a study conducted by Saskın et al., the effect of preoperatively calculated PLR value on postoperative outcomes in patients who underwent CABG was investigated. In this study, preoperative high PLR values were found to be associated with early atrial fibrillation, prolonged intensive care durations, neurological events and mortality [19]. In another study conducted in this direction, high PLR value was determined as an independent predictor for postoperative atrial fibrillation [20]. In a recent study done by Navani et al., no relationship was determined between PLR value and early atrial fibrillation, stroke, prolonged ventilation, postoperative myocardial infarction and mortality in patients who underwent CABG [21]. In our study, although the preoperative NLR value for MACCE was an independent predictor, PLR value was not correlated with MACCE.

Recently, the SII value obtained from thrombocyte, neutrophil and lymphocyte values has been used as a prognostic marker in other fields of medicine. This parameter was first defined by Hu et al in 2014. In that study, it was shown that it is related to bad prognosis in patients with hepatocellular cancer and that it can be used in determining treatment strategies [22].

In a study conducted in the cardiovascular field, coronary artery patients, who had 5602 percutaneous coronary interventions, were included. In this study, the predictive role of SII in predicting major adverse cardiac events after PCI was investigated. High SII values were found to be associated with cardiac death, fatal stroke and nonfatal stroke. At the end of the study, the authors emphasized that the SII value in CAD patients undergoing PCI is more predictive than known risk factors [23]. In a recent study conducted by Dey et al., the role of SII value in predicting postoperative bad outcomes in patients, who underwent off-pump CABG operation was investigated. At the conclusion of the study, the authors determined the SII value as an independent predictor for predicting postoperative poor outcomes. In addition, high inotropic support was found to be associated with poor postoperative outcomes [8]. In our study, SII value was determined as an independent predictor for postoperative MACCE. Also, a correlation between increased use of inotropic agents and MACCE were found.

Prognostic nutritional index is an important parameter obtained from lymphocyte and albumin values and an indicator of malnutrition status. The bad prognostic effect of low lymphocyte in cardiovascular diseases is known. Albumin, on the other hand, is a protein that has anti-inflammatory and antioxidant effects as well as effects on osmotic pressure. Therefore, a low albumin rate is a poor prognostic condition for cardiovascular diseases [24]. In line with this information, low PNI value appears as a poor prognostic marker. The effect of PNI value on postoperative outcomes was investigated in a retrospective study by Lee et al., in which patients, who underwent open heart surgery with CPB, were included. At the end of the multivariate analysis performed in this study, low PNI value, high CPB duration and advanced age were determined as independent predictors for early postoperative complications [25]. Low PNI value was also found as an independent predictor for development of MACCE in our study.

LIMITATIONS OF THE STUDY

The most important limitation of our study is that it is a single center retrospective study, as a result, the number of patients was also limited. In addition, the inequality of age groups is another limitation. The effects of highly sensitive CRP, procalcitonin and interleukin 6 and similar inflammatory parameters could not be evaluated due to the retrospective design of the study. Although prognostic nutritional index is a simple calculable indicator of malnutrition status, studies with a large number of patients are needed to fully elucidate the mechanism of its effect on bad results.

CONCLUSION

It is particularly important to anticipate the risks of complications after coronary bypass operations. Therefore, in addition to various risk scoring systems, various inflammatory biomarkers have also been studied. In this current study, it was demonstrated that SII and PNI values, which are among the inflammatory parameters and which can be obtained cheaply and easily, may be good predictors for MACCE emerging after CABG operations.

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RESEARCH ARTICLE

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The Effect of the COVID-19 Pandemic on the Epidemiology of Hip Fractures

Kalça kırıklarının epidemiyolojisine Covid-19 pandemisinin etkisi

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ABSTRACT

Aim: This study aimed to compare the epidemiology of hip fractures in an elderly population in 6 months of the COVID-19 pandemic and the same 6-month period in the previous year to be able to reveal how the decrease in community activity beyond normal seasonal habits because of the pandemic had affected the incidence of fractures in the elderly patient population.

Methods: A comparison was made of the data of patients who presented at our hospital with a hip fracture between 1 April 2020 and 30 September 2020, and those who presented in the same 6-month period in 2019 before the pandemic. Comparisons were made in respect of epidemiology, treatments applied, complication rates and mortality. The demographic data of the patients were examined, and those presenting during the pandemic were evaluated in respect of the presence of COVID-19 infection.

Results: A total of 78 patients were treated in the defined study period in 2020 and 71 in the equivalent period in 2019 before the pandemic. No statistically significant change was found in the number of hip fractures in 2020 ($p>0.05$). No statistically significant difference was observed between the demographic data of the patients, the ASA scores, the treatment methods, or the mortality rates in the two periods **($p>0.05$ for all).**

Conclusions: The most significant finding of this study was that there was no decrease in the number of patients with hip fracture during the pandemic in 2020, compared to the equivalent period in 2019. The increase in pulmonary complications during the pandemic period demonstrates the need for special care conditions in elderly patients with hip fractures, which are still seen at a high rate despite the pandemic.

Keywords: Coronavirus, Hip fractures, pandemic

ÖZ

Amaç: Normal mevsimsel sürenin ve normal insan alışkanlıklarının ötesinde toplum aktivitesi azalmasının, yaşlı hasta popülasyonunda görülen kırıkların insidansının nasıl etkilediğini ortaya koymak için pandeminin 6 aylık dönemindeki kalça kırıklarının epidemiyolojisini, bir önceki yıldaki aynı 6 aylık zaman aralığına göre karılaştırmayı ve pandemiye bağlı değişiklikleri ortaya koymayı amaçladık.

Yöntemler: Çalışmamızda 1 Nisan 2020 ile 30 Eylül 2020 tarihleri arasındaki pandeminin 6 aylık süresi zarfında hastanemize başvuran kalça kırıkları ile 2019 yılının aynı döneminde hastanemize başvuran kalça kırıkları, epidemiyolojileri ve uygulanan tedaviler, komplikasyon oranları ve mortalite yönünden karşılaştırıldı. Hastaların demografik verilerine bakıldı. Pandemi döneminde kalça kırığı ile başvuran hastaların eşlik eden COVID 19 enfeksiyonu olup olmadığı değerlendirildi.

Bulgular: Pandemi öncesi 2019 yılında 71 hasta tedavi edilirken 2020 yılında 78 hasta tedavi edilmişti. 2020 yılında kalça kırık sayısının istatistiksel olarak değişmediği bulundu ($p>0.05$). Tedavi yöntemleri açısından istatistiksel olarak anlamlı fark gözlenmedi ($p>0.05$). 2019 ve 2020 yılları arasında demografik verileri açısından istatistiksel olarak anlamlı fark saptanmamıştır ($p>0.05$). 2019 ve 2020 yılları arasında hastaların ASA skorları açısından anlamlı fark saptanmamıştır ($p>0.05$). 2019 ve 2020 yılları arasında mortalite oranları açısından anlamlı fark saptanmamıştır ($p>0.05$).

Sonuçlar: Çalışmamızın en önemli bulgusu 2020 yılında pandemi döneminde kalça kırığı olan hasta sayısının 2019 yılına göre düşmemesidir. Pandemi döneminde pulmoner komplikasyonlardaki artış, yaşlı hasta popülasyonunda pandemiye rağmen yüksek oranda görülen kalça kırıklı hastalarda özel bakım şartlarının gerekliliğini ortaya koymaktadır.

Anahtar Kelimeler: coronavirus, kalça kırıkları, pandemi

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INTRODUCTION

Following the outbreak of the novel coronavirus (SARS-CoV-2) determined as an agent of pneumonia resulting in death, Wuhan, China, in December 2019, the coronavirus disease 2019 (COVID-19) spread rapidly around the world and was declared a global pandemic by the World Health Organisation on 11 March 2020. The first case in Turkey was recorded on 11 March 2020. With no preventative vaccination or definitive treatment, Turkey and the whole world started to implement quarantine precautions with the closure of public spaces and curfews [1].

The COVID-19 pandemic caused by the SARS-CoV-2 virus had a significant effect on life throughout the whole world. People had to abandon various social habits because of quarantine, and by spending more time at home, activity levels significantly decreased [2,3] This decreased level of activity has been reported to reduce the incidence of several fractures [1, 4]. However, there are also reports in literature that the rate of hip fractures in the elderly population, which are generally the result of a fall in the home, has not changed [4].

Hip fractures have high mortality and morbidity in the elderly patient population [5,6]. SARS-CoV-2 virus infection is known to lead to more severe disease and higher mortality rates in the elderly population. Hip fracture mortality rates in the elderly population have been reported to have increased during the COVID-19 pandemic [7]. The outcomes have shown differences between countries and hospitals according to the effects of the pandemic and population distribution [8, 9].

Therefore in this study, the incidence of hip fractures seen in an elderly patient population in a 6-month period of the pandemic were evaluated to reveal the effect of reduced community activity beyond the normal seasonal habits. This study aimed to compare the incidance of hip fractures in a 6-month period of the pandemic with the equivalent 6-month period in the previous year, to determine changes related to the COVID-19 pandemic.

MATERIAL AND METHOD

The first case of COVID-19 was recorded on 11 March 2020, and from that date, quarantine precautions started to be implemented throughout the whole country. In the study, patients who presented at our hospital with a proximal femur fracture in the 6-month pandemic period of 1 April 2020 – 30 September 2020, were compared with patients who presented in the equivalent period in 2019 in respect of the treatments applied and complication rates.

The study included all patients aged >65 years with a fracture of 31A, 31B, and 31C according to the AO classification (Figure 1). Patients with a pathological fracture, periprosthetic fracture or multiple fractures were excluded from the study. A total of 154 patients with hip fractures were identified in the defined 6-month periods of 2019 and 2020. A total of 5 patients were excluded due to the unavailability of data of hip radiographs at the time of presentation, BMI, or operation data.

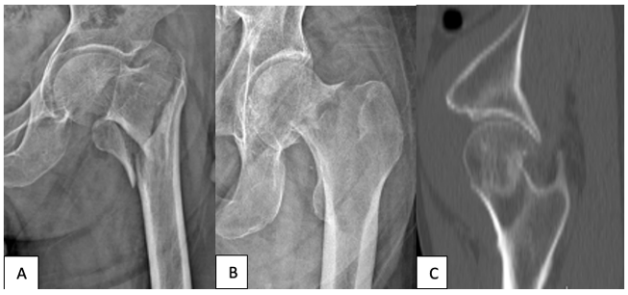

Figure 1. Anteroposterior radiograph of an 84-year old female patient with 31A fracture (A), anteroposterior radiograph of a 74-year old male patient with 31B fracture (B), and Computed tomography slice of a 81-year old male patient with 31C fracture (C).

The data of patients with a hip fracture were retrieved from the hospital electronic database according to the defined study criteria. The patients were evaluated in respect of age, gender, body mass index (BMI), date of presentation, fracture side and fracture type. The treatment methods applied to the patients were also examined (conservative or which surgical method), the American Society of Anaesthesiologists (ASA) scores of the patients treated surgically, the presence of COVID-19 infection, whether or not there were findings on pulmonary radiographs of acute pulmonary complications requiring oxygen support preoperatively or postoperatively, time from admission to surgery, anesthesia type, a requirement for intensive care, the presence

of venous thromboembolism, dislocation, deep infection in the operation site, and in-hospital mortality rates.

Approval for the study was granted by the Local Ethics Committee.

Statistical Analysis

Data obtained in the study were analyzed statistically with IBM SPSS vn. 25.0 software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). Conformity of the data to normal distribution was assessed with the Shapiro Wilk test. To compare variables in groups of nonparametric data, the Mann Whitney U-test was applied. For the comparison of categorical data, the Chi-square test was used. A value of $p<0.05$ was accepted as statistically significant for all the parameters.

RESULTS

A total of 154 patients with hip fractures were identified in the defined 6-month periods of 2019 and 2020. A total of 5 patients were excluded due to the unavailability of data of hip radiographs at the time of presentation, BMI, or operation data. Thus, the study included 149 patients, as 71 in 2019, and 78 in 2020. There was found to be no change in the frequency of hip fractures seen in 2020 compared to 2019 (p=0.99). The demographic data of the patients are shown in Table 1. No statistically significant difference was determined between the patient groups of both years in respect of age (p=0.97).

The distribution of patients according to age and date of presentation is shown in Figure 2. No significant difference was determined between 2019 and 2020 in respect of in-hospital mortality rates (p=0.56). Mortality developed in 5 (7%) patients during hospitalization in the study period of 2019, and 8(10%) patients in 2020.

When the patients who presented at the Emergency Department with a hip fracture in 2019 and were planned to undergo surgical treatment were evaluated in respect of ASA scores, ASA 2 was determined in 35 (50.7%) patients, ASA 3 in 30 (43.5%), and ASA 4 in 4 (5.8%). In 2020, the ASA scores were ASA 2 in 38 (50.7%) patients, ASA 3 in 32 (43%) and ASA 4 in 5 (6.3%). No statistically significant difference was determined between the two-year groups of patients in respect of ASA scores (p=0.976). Of the patients who presented during the pandemic in 2020, no COVID-19 test was applied to 24 (30.8%) patients, COVID-19-positivity was determined in 8 (10.2%) patients, and the test was negative in 46 patients.

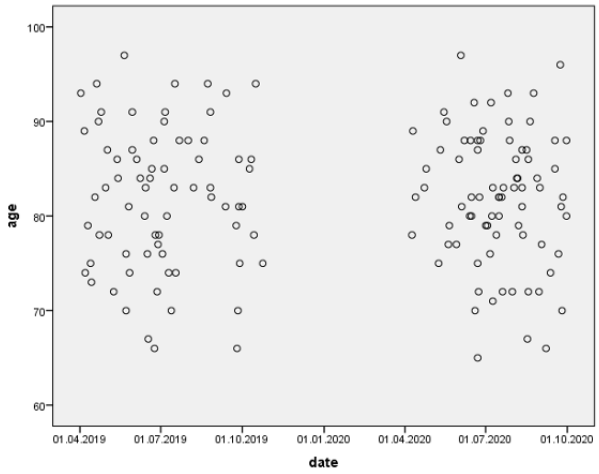

Figure 2. Chart of the patients presentation at hospital according to the date and age in 2019 and 2020

Of the patients with a positive COVID-19 test, conservative treatment was applied to 2 patients and 3 patients with a mean age of 81 years were re-tested and on obtaining a negative result, were operated on at mean 12.3 days later. Of these, mortality was observed in 1 patient. In 1 patient, respiratory failure developed, and after follow-up in the Intensive Care Unit (ICU), this patient was discharged on the 17th day. In the third patient, no symptoms were observed during follow-up and the patient was discharged on the 11th day. The other results of the patients in 2019 and 2020 are summarised in Table 2.

Table 1. Demographic data

	2019		2020		p value
Mean age (years)	Mean	SD	Mean	SD	
	81.94	7.5	81.88	7	0.970
Number of patients	71		78		
Gender	39.4% Male	60.6% Female	42.3% Male	57.7% Female	0.425
Side	46.5% Right	53.5% Left	41% Right	59% Left	0.307
BMI (body mass index)	26.73	3.5	26.44	3.3	0.438

Table 2: Results of the 2019 and 2020 groups

Variable	2019		2020		P value
Fracture type					0.474
31A	41 (57.7%)		48 (61.5%)		
31B	19 (26.8%)		23(29.5%)		
31C	11 (15.5%)		7 (9%)		
Treatment					0.788
Conservative	2 (2.8%)		3 (3.8%)		
Partial prosthesis	50 (70.4%)		59 (75.6%)		
Cannulated screw	6 (8.5%)		4 (5.1%)		
Proximal femoral nail	13 (18.3%)		12 (15.4%)		
Anaesthesia type					0.936
Spinal	66 (93.0%)		72 (92.3%)		
General	3 (4.2%)		3 (3.8%)		
Time from admission to operation (days)	Mean	SD	Mean	SD	0.101
	2.26	1.73	2.19	2.7	
Length of stay in hospital (days)	6.18	3.21	6.34	4.28	0.632
Pulmonary complications	7		12		
Venous thromboembolism	3		3		
Dislocation	1		0		
Deep tissue infection	2		3		
Intensive Care Unit admission	24		29		
Mortality	5		8		

DISCUSSION

The most significant finding of this study was that the incidence of hip fractures did not decrease during the COVID-19 pandemic. Although a decrease in the incidence of fracture of several bones has been reported to be related to reduced activity, it is a common finding that hip fracture incidence was not decreased in the pandemic [4,7,8,10]. Lv et al reported that the incidence of fractures in general was lower in a 1-month period of the pandemic compared to the previous year [10]. A more recent study also reported that the general incidence of fractures decreased in a period of approximately 40 days in the pandemic [1]. In a study by Nunez et al, although it was reported that the incidence of fractures in an 80-day pandemic period was lower than the incidence of traumatic fractures in 4 periods of 20 days in the previous year, the incidence of hip fractures was not decreased, as in the current study [11]. No study could be found in literature which compared how fracture incidence had changed in a 6-month period of the pandemic, and the longest study that could be found was of an 80-day period [4].

The adoption of more sedentary lifestyle habits of people under prolonged quarantine conditions leads to a reduction in body muscle mass, and an increase in fatty tissue and BMI [12]. Another result of reduced physical activity is osteoporosis [13]. Increased BMI alone variable when taken as a factor, it reduces the risk of fractures[14]. But in people with the same bone mineral densitometry Increased BMI has been shown to increase fracture risk [15].Together with the increased risk of fracture, the postoperative complication rate has also been reported to increase in individuals with high BMI [16].

It is known that the patient group where mortality is seen most with pneumonia in COVID-19 infection is the elderly population [17]. In parallel with this, it has been reported that mortality rates have increased during the pandemic without a change in the incidence of hip fractures [8]. Another study reported that there was no change in the hip fracture incidence and mortality rates during the pandemic [7]. In the current study, a numerical increase was seen in mortality rates but this numerical increase was not statistically significant. In a study conducted in 2019 immediately before the pandemic, the in-hospital mortality rate of patients with hip fracture was found to be 3%, and the most common cause of death was reported to be respiratory failure [18]. From this finding, COVID-19 pneumonia can be expected to increase the in-hospital mortality rates of patients with hip fractures.

The current study results showed that the time to surgery of the COVID-19-negative patients in 2020 was shorter compared to the patients in 2019, but the difference was not statistically significant. The time to surgery of the patients preoperatively determined with COVID-19 positivity was found to be statistically significantly longer than that of the COVID-19 negative patients. Although the time to surgery of the COVID-19-negative patients was found to be shorter compared to 2019, no statistically significant reduction was determined. Early surgery and therefore a shorter length of stay in hospital for COVID-19 negative patients is a recommended method to protect the patients

and their families from COVID-19 infection [19].

In a multi-center study conducted immediately before the pandemic, the outcomes were compared of hip fracture patients applied with an accelerated surgical procedure, patients applied with early surgery and those applied with the standard surgical procedure. The mortality rates were not seen to change in the patients applied with accelerated surgery [20]. A multicentre study of 146 hip fractures during the pandemic reported that mortality rates were increased in patients with delayed surgery and in those treated conservatively [21]. However, no study could be found in literature showing the effect on mortality rates of early surgery applied to patients with COVID-19 positivity, or showing any algorithm for the timing of surgery in these patients.

There were some limitations to this study, primarily that it was conducted in a single center and relatively few patients were evaluated. Therefore, there is a need for further multicentre studies. However, this present study may contribute to national data and/or the systematic reviews and meta-analyzes [22] which will be done together with other studies originating from our country about ıssue. As bone mineral density values were available for very few of the current study patients, bone mineral density results could not be included in the evaluations. Furthermore, no evaluations could be made of follow-up and mortality rates after discharge, or complications which developed during home care. There was also no evaluation of the mechanism of fracture (fall at home, etc).

CONCLUSION

Under prolonged pandemic conditions, there is a tendency for more sedentary lifestyle habits, especially in the elderly population. Consequently, decreasing bone quality and increasing BMI are factors increasing the possibility of fracture. To prevent this, it can be recommended that during a period of pandemic there is a need for home exercise programs to be established, and environments should be provided for people to protect their health by leaving their home and taking physical exercise. The creation of a treatment algorithm for the pandemic period specific to the elderly patient group with fractures, primarily hip fracture patients, would be useful in the more productive use of limited economic and human resources, and in the determination of more effective treatment strategies.

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Evaluation of inflammation in obesity and chronic kidney disease with hemogram parameters

Obezite ve Kronik Böbrek Hastalığındaki İnflamasyonun Hemogram Parametreleri ile Değerlendirilmesi

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ABSTRACT

Aim: Chronic inflammation is involved in the pathogenesis of both obesity and chronic kidney disease (CKD). We aimed to evaluate the parameters derived from complete blood count (CBC) as inflammatory markers in obese patients and obese CKD patients.
Methods: Individuals enrolled in the study were divided into three groups. Group-1 was composed of obese patients; group-2 was composed of obese CKD patients and group-3 was composed of healthy individuals as the control group. This study was conducted at a training and research hospital over 6 months period.
Results: Forty-one patients were in group-1; 41 patients were in group-2 and 22 individuals were in group-3. White blood cell count (WBC) was significantly higher in group-1 and group-2 compared with group-3 (7,5±1,4 x103/μL vs 8,4±2,4 x103/μL vs 6,5±1,3 x103/μL, respectively, p<0.001) and neutrophile to lymphocyte ratio (NLR) was significantly higher in group-1 and group-2 compared with group-3 (1,9±0,7 vs 2,5±1,5 vs 1,7±0,4, respectively, p<0.001). NLR and WBC was found positively correlated with systolic blood pressure, urea, creatinine, uric acid, whereas negatively correlated with estimated glomerular filtration rate.
Conclusions: It is important to determine significant results in CBC derived markers that are widely used in routine clinical practice as inflammatory markers.

Keywords: Inflammation, Renal Insufficiency, Blood cell count.

ÖZ

Amaç: Kronik inflamasyon hem obezitenin hem de kronik böbrek hastalığının patogenezi ile ilişkilidir. Çalışmamızda obez hastalarda ve obez kronik böbrek hastalarında inflamasyon belirteci olarak tam kan sayımı parametrelerinin değerlendirilmesini amaçladık.
Yöntemler: Çalışmada yer alan bireyler 3 ayrı gruba bölündü. Grup-1 obez hastalardan, grup-2 obez kronik böbrek hastalarından, grup-3 kontrol grubu olarak sağlıklı bireylerden oluşmakta idi. Çalışmamız, 6 aylık bir sürede bir eğitim ve araştırma hastanesinde gerçekleştirildi.
Bulgular: Kırkbir hasta grup-1'de; 41 hasta grup-2'de ve 22 sağlıklı birey grup-3'de yer aldı. Beyaz küre sayıları grup-3'e kıyasla grup-1 ve grup-2'de anlamlı düzeyde yüksek saptandı (7,5±1,4 x103/μL vs 8,4±2,4 x103/μL vs 6,5±1,3 x103/μL, sırasıyla, p<0.001) ve nötrofil lenfosit oranı grup-3'e kıyasla grup-1 ve grup-2'de anlamlı düzeyde yüksek saptandı (1,9±0,7 vs 2,5±1,5 vs 1,7±0,4, sırasıyla, p<0.001). Nötrofil lenfosit oranı ve beyaz küre sayısının, sistolik kan basıncı, ürik asit, üre ve kreatinin arasında pozitif; glomerüler filtrasyon hızı ile negatif korelasyon saptandı.
Sonuçlar: Rutin klinik pratikte sıkça kullanılan hemogramdan elde edilen parametrelerin inflamasyon belirteçleri olarak anlamlı sonuçlanması önemlidir.

Anahtar Kelimeler: İnflamasyon, Böbrek Yetmezliği, Kan Hücre Sayımı.

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INTRODUCTION

Inflammation is the basis for the pathogenesis of numerous diseases. Determination of the inflammatory state is essential in following the course of the disease, as well as in evaluating the response of treatment in inflammatory diseases. Unless properly regulated, inflammation and oxidative stress can cause devastating effects such as excessive cytokine production, increase in pro-inflammatory and oxidative stress mediators [1]. Obesity is defined as the positive energy balance resulting from the imbalance between energy intake and consumption [2]. Many pro-inflammatory and anti-inflammatory molecules, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α), are known to be produced and released from adipose tissue [3]. Obesity has both direct and indirect effects on chronic kidney disease development. Compensatory hyperfiltration occurs in obese patients in order to meet the increased metabolic needs resulting from the increased body weight. In the long term, this condition results in CKD development via an increase in intraglomerular pressure and damage in the kidney structure. Moreover, inflammation and oxidative stress have been found to be associated with CKD progression in studies in the literature [4]. CBC testing is a widely used laboratory test in clinical practice and there are various clinical studies that demonstrate the association between inflammatory states in conditions such as infections, sepsis, tumoral and rheumatological diseases and parameters that derived from CBC testing, such as monocyte to lymphocyte ratio (MLR) neutrophile to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) [5-7]. In this study, we aimed to evaluate the parameters derived from CBC as inflammatory markers in obese patients and obese CKD patients.

MATERIAL and METHOD

Study Design

The study was approved by the institutional ethics committee on the date of March 21, 2018 with the approval number [8]. This study was conducted in the out-patient clinic of the department of nephrology at two training and research hospitals, over a 6 month period. Patients under 18 years old, those with acute infection, malignancy, congestive heart failure, chronic obstructive lung disease, diabetes mellitus and acute and or chronic liver disease, were excluded from the study. All of the patients included in the study signed informed consent. Individuals enrolled in the study were divided into three groups: Group-1 was composed of obese patients, Group-2 was composed of obese CKD patients and Group-3 was composed of healthy individuals, as the control group. Estimated glomerular filtration rate (eGFR) was calculated by the CKD Epidemiology Collaborative Study Equation [8]. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline was used to determine the kidney function stage [9]. Body mass index (BMI) was calculated from the formula weight(kg)/height 2(m2). Obesity is defined as BMI greater or equal than 30 kg/m2 [10].

Laboratory Assessment

Laboratory results of patients, including glucose, urea, creatinine, eGFR, uric acid, albumin, ALT (alanine aminotransferase), AST (aspartate aminotransferase), cholesterol, low density lipoprotein (LDL) and CBC , were obtained from their most recent medical records. NLR, PLR and MLR were calculated by dividing neutrophil count to lymphocyte count, platelet count to lymphocyte count and monocyte count to lymphocyte count, respectively.

Statistical Analysis

Continuous parametric variables were represented as means ± standard deviation. Categorical variables were represented as percentages. The Chi-square and Fisher Exact test were used to compare categorical variables. Non-parametric continuous variables were represented as median with 25-75 interquartile range. Comparison of the means of numerical variables of more than two independent groups was made using the One-Way ANOVA test and the post-hoc Bonferroni test was used to determine if the groups were significantly associated. The relationship between NLR and WBC and other demographic and laboratory data was done using Pearson's correlation analysis. The SPSS 18.0 program (Chicago, IL USA) was used to perform all statistical analyses. In our study, $p < 0.05$ was considered significant.

RESULTS

Forty-one patients were in group-1, 41 patients were in group-2 and 22 individuals were in group-3. According to the KDIGO clinical practice guideline, 32 CKD patients (78%) in group-2 were in stage-3 and 9 CKD patients (22%) in group-2 were in stage-4. There was no statistically significant difference between groups in terms of age (44±9,8 years vs 46±5,5 years vs 42±9,5 years; p=0.432) and gender (73/27 F/M% vs 58/42 F/M% vs 59/41 F/M%; p=0.323), respectively. BMI was significantly higher in group-1 and group-2 compared with group-3 (36±3 kg/m2 vs 35±3 kg/m2 vs 27±5, respectively, p<0.001). Serum urea levels were significantly higher in group-2 compared with group-1 and group-3 (26±7 mg/dl vs 62±34 mg/dl vs 29±6 mg/dl, respectively, p<0.001). Serum creatinine levels were significantly higher in group-2 compared with group-1 and group-3 (0,9±0,1 mg/dl vs 1,8±0,5 mg/dl vs 0,9±0,2 mg/dl, respectively, p<0.001) and eGFR was significantly lower in group-2 compared with group-1 and group-3 (84±17 ml/min/1.73m2 vs 39±13 ml/min/1.73m2 vs 90±15 ml/min/1.73m2, respectively, p<0.001).

Serum uric acid levels were significantly higher in group-1 and group-2 compared with group-3 (5,5±1,5 mg/dl vs 7,7±1,7 mg/dl vs 4,6±0,9 mg/dl, respectively, p<0.001). Serum ALT levels were significantly higher in group-1 and group-2 compared with group-3 (26±12 IU/L vs 20±10 IU/L vs 19±6 IU/L, respectively, p<0.001) and serum AST levels were significantly higher in group-1 and group-2 compared with group-3 (24±8 IU/L vs 22±9 IU/L vs 19±5 IU/L, respectively, p<0.001), as well. Serum hemoglobin levels were significantly lower in group-2 compared with group-1 and group-3 (14±1,5 g/dL vs 13±1,8 g/dL vs 14±1,6 g/dL, respectively, p<0.001).

Systolic blood pressure (SBP) levels were significantly higher in group-1 and group-2 compared with group-3 (122±11mmHg vs 142±21 mmHg vs 122±10 mmHg, respectively, p<0.001); diastolic blood pressure (DBP) levels were significantly higher in group-1 and group-2 compared with group-3 (80±7mmHg vs 89±14 mmHg vs 78±9 mmHg, respectively, p<0.001) and mean blood pressure (MBP) levels were significantly higher in group-1 and group-2 compared with group-3 (99±8mmHg vs 114±15 mmHg vs 97±8 mmHg, respectively, p<0.001). Demographical data and laboratory results of groups are presented in Table.1.

Table.1 Demographical and Laboratory Results of groups 1, 2 and 3.

	Group-1 (n=41)	Group-2 (n=41)	Group-3 (n=22)	p
Age (years)	44±10	46±6	42±9	0.43
Gender F/M (%)	73/27	59/41	59/41	0.32
BMI (kg/m2)	36±3	35±3	27±5	0.00 **, ***
Glucose (mg/dl)	91±8	96±13	93±10	0.09
Urea (mg/dl)	26±7	62±34	29±6	0.00 *, ***
Creatinine (mg/dl)	0,9±0,1	1,8±0,5	0,9±0,2	0.00 *, ***
eGFR (ml/min/1.73m2)	84±17	39±13	90±15	0.00 *, ***
Uric Acid (mg/dl)	5,5±1,5	7,7±1,7	4,6±0,9	0.00 *, ***
Albumin (g/dl)	4,4±0,2	4,3±0,4	4,3±0,3	0.38
ALT (IU/L)	26±12	20±10	19±6	0.00 **, ***
AST (IU/L)	24±8	22±9	19±5	0.04 **, ***
Cholesterol (mg/dL)	213±36	222±61	201±47	0.28
LDL (mg/dL)	139±28	146±45	130±37	0.28
SBP (mmHg)	122±11	142±21	122±10	0.00 **, ***
DBP (mmHg)	80±7	89±14	78±9	0.00 **, ***
MBP (mmHg)	99±8	114±15	97±8	0.00 **, ***

Abbreviations: NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; MLR: Monocyte to Lymphocyte Ratio; BMI: Body Mass Index; eGFR: estimated glomerular filtration ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDL: Low density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure.

Notification: Statistically significant difference between Group-1 and Group-2 is defined with the marker *; statistically significant difference between Group-1 and Group-3 is defined with the marker **; statistically significant difference between Group-2 and Group-3 is defined with the marker *.**

WBC was significantly higher in group-1 and group-2 compared with group-3 (7,5±1,4 x103/µL vs 8,4±2,4 x103/µL vs 6,5±1,3 x103/µL, respectively, p<0.001) and NLR was significantly higher in group-1 and group-2 compared with group-3 (1,9±0,7 vs 2,5±1,5 vs 1,7±0,4, respectively, p<0.001). Inflammation markers derived from CBC, are presented in Table.2.

In the Pearson correlation analysis, NLR was positively correlated with SBP, DBP, MAP, urea, creatinine, uric acid and WBC, whereas negatively correlated with eGFR, ALT and hemoglobin. On the

other hand, WBC was found positively correlated with BMI, SBP, urea, creatinine, uric acid, AST, hemoglobin and NLR, whereas negatively correlated with eGFR. Pearson correlation analysis of NLR and WBC is presented in Table.3.

Table.2 Complete Blood Count Parameters in terms of inflammation markers.

	Group-1 (n=41)	Group-2 (n=41)	Group-3 (n=22)	p
White Blood Cell (x103/μL)	7,5±1,4	8,4±2,4	6,5±1,3	0.00 **, ***
Hemoglobin (g/dL)	14±1,5	13±1,8	14±1,6	0.01 *, ***
NLR	1,9±0,7	2,5±1,5	1,7±0,4	0.00 **, ***
PLR	125±50	135±43	111±29	0.06
MLR	0,23±0,1	0,23±0,1	0,19±0,01	0.14

Abbreviations: NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; MLR: Monocyte to Lymphocyte Ratio
Notification: Statistically significant difference between Group-1 and Group-2 is defined with the marker *; statistically significant difference between Group-1 and Group-3 is defined with the marker **; statistically significant difference between Group-2 and Group-3 is defined with the marker *.**

Table.3 Pearson's Correlation Analysis of NLR and WBC

	NLR		WBC (x10³/μL)	
	Rh0	p	Rh0	p
BMI (kg/m2)	-	-	0.503	0.000
SBP (mmHg)	0.310	0.001	0.199	0.043
DBP (mmHg)	0.216	0.027	-	-
MBP (mmHg)	0.295	0.002	-	-
Urea (mg/dl)	0.484	0.000	0.311	0.001
Creatinine (mg/dl)	0.580	0.000	0.381	0.000
eGFR (ml/min/1.73m²)	-0.427	0.000	-0.293	0.003
Uric Acid (mg/dl)	-	-	0.220	0.025
Hemoglobin (g/dL)	-0.277	0.004	0.889	0.000
WBC (x103/μL)	0.456	0.000	-	-
NLR	-	-	-0.277	0.004

Abbreviations: NLR: Neutrophil to Lymphocyte Ratio; BMI: Body Mass Index; eGFR: estimated glomerular filtration ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure; WBC: White Blood Cell Count.

Notification: Only significant results are presented.

DISCUSSION

In the present study, we evaluated CBC derived parameters such as WBC, NLR, PLR and MLR as markers of inflammation in obese patients and obese CKD patients. Although a statistically significant difference was found only for NLR and WBC, all of the markers derived from CBC such as WBC, NLR, PLR and MLR were found higher in obese patients and obese CKD patients, compared with healthy individuals. It is essential to determine the significance of CBC derived markers that are widely used in routine clinical practice as inflammatory markers.

Obesity can result in a pro-inflammatory state via both increasing levels of pro-inflammatory cytokines and diminishing levels of anti-inflammatory cytokines and in the literature, obesity was found associated with chronic inflammation [11]. On the other hand, the absence of CKD in most obese patients indicates that weight gain alone does not lead to CKD development. Obesity is thought to contribute to the underlying inflammatory process in chronic kidney disease and as a result, increased oxidative stress and inflammatory process further increase the risk of CKD [12]. In our study, consistent with the findings in the literature, we found higher levels of CBC derived inflammatory markers such as WBC, NLR, PLR, MLR, and lower levels of eGFR in obese patients and obese CKD patients, compared with healthy individuals. The lack of statistically significance between groups in terms of MLR and PLR may be due to the insufficient number of patients in the study.

Plasma uric acid levels are increased in CKD due to a decrease in eGFR. In addition to CKD, an increase in serum uric acid levels is associated with many conditions, including obesity [13]. Although the underlying mechanism of uric acid increase in obesity has not been precisely identified, hyperuricemia may occur via an increased urate production, decreased renal clearance and reduced renal excretion [14]. The association between hyperuricemia and CKD progression still remains controversial. Jurascheck et al. found that hyperuricemia is more frequent in patients with reduced eGFR [15]. Russo et al. similarly reported hyperuricemia associated with CKD progression [16]. On the other hand, in some studies, such as the study conducted by Nakayama et al., the association between hyperuricemia and CKD progression could not be clearly demonstrated [17]. Sum of all, although some conflicting results exist about the relationship between hyperuricemia and CKD development and progression, data from comprehensive range studies support the relationship between them [18,19]. In

addition, in another study, uric acid was found to induce inflammation and to be associated with inflammatory markers [20]. In our study, similarly, we found the highest uric acid levels in obese CKD patients, followed by the obese patients and the healthy control group, respectively. A positive correlation was also found between uric acid and WBC as an inflammatory marker derived from CBC. It can also be speculated from our results that the underlying inflammation in obesity and CKD, might have contributed to the elevation in uric acid levels in the patient groups.

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in adults, whose prevalence between diabetic and obese individuals is around 80% compared to 30-50% of the general population and mildly elevated aminotransferase (ALT and AST) levels are the most common laboratory findings of NAFLD [21]. In our study, according to the literature results, we found mildly elevated aminotransferase levels both in obese patients and obese CKD patients.

It is a well-known fact that obesity is associated with higher blood pressure levels [22]. The role of inflammation in the pathophysiology of hypertension is suggested from the findings in the literature [23]. In our study, we found the highest blood pressure levels in obese CKD patients, followed by obese patients. In addition, we found a positive correlation between inflammation markers and blood pressure levels. Our results may suggest the association between inflammation and hypertension, both in obese patients and obese CKD patients.

CONCLUSION

Obesity and CKD are both chronic conditions that share common pathophysiological mechanisms, including inflammation. Although many inflammatory markers had been defined, simple and accessible examinations such as CBC derived markers stand out with their widespread use and easy accessibility, in monitoring both the disease course and the effectiveness of treatment strategies.

LIMITATIONS

First, the total number of individuals enrolled in the study was small. Second, although the central aim of the study was to evaluate CBC-derived markers, we also aimed to compare other commonly used inflammatory markers, such as c-reactive protein (CRP), between groups. However, we could not evaluate other markers as a result of technical problems developed during the study.

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Heparin titration protocol with tranexamic acid in cardiac surgery: a pilot study

Kalp Cerrahisinde Traneksamik Asit ile Beraber Heparin Titrasyon Protokolü Kullanımına Yönelik Bir Pilot Çalışma

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ABSTRACT

Aim: Postoperative bleeding related to cardiac surgery is a clinically important condition. Consequently, re-exploration and increased blood utilization lead to adverse outcomes. The aim of this pilot study was to assess the effect of a newly adapted blood conservation strategy, including heparin titration protocol along with antifibrinolytics, regarding to mediastinal bleeding, re-exploration for bleeding and blood and blood products utilization.

Methods: This study included 100 patients undergoing cardiac surgery with higher risk for bleeding, such as mitral valve replacement, aortic valve replacement, ascending / arcus aortic surgery, between January 2015 and August 2016. The study group consisted of consecutive patients who underwent new protocol (heparin titration protocol + tranexamic acid). The control group consisted of patients who were administered standard dose heparin(4 mg/kg). Fifty patients in each group (with the new protocol and the standard protocol) were compared by means of amount of heparin applied, blood utilization, mediastinal drainage and rate of re-exploration.

Results: Twenty-eight of the 50 study group patients (56%) received a red blood cell (RBC) transfusion for the first 24 hours. RBC transfusion ≥ 3 units was lower in the study group (34% vs 54%; p=0.044). Moreover, mediastinal drainage and blood utilization was found to be lower at the study group, however re-exploration rates remained similar.

Conclusion: Based on our study results, the suggested heparin titration protocol seemed to be beneficial for reducing postoperative bleeding and blood product usage. We consider that blood utilization protocols like our heparin titration protocol should be established to reduce the need for blood transfusion in cardiac surgery.

Keywords: Cardiac surgery; blood transfusion; drainage; reoperation; heparin; tranexamic acid.

ÖZ

Amaç: Kalp cerrahisi ile ilişkili postoperatif kanama klinik olarak önemli bir durumdur. Sonuç olarak, reeksplorasyon ve artan kan kullanımı olumsuz sonuçlara yol açar. Bu pilot çalışmanın amacı, mediastinal kanama, kanama sebepli reeksplorasyon ve kan-kan ürünü kullanımına ilişkin antifibrinolitikler ile birlikte heparin titrasyon protokolünü içeren yeni uyarlanmış bir kan koruma stratejisinin etkisini değerlendirmektir.

Yöntemler: Bu çalışmaya Ocak 2015 ile Ağustos 2016 tarihleri arasında mitral kapak replasmanı, aort kapak replasmanı, asendan/arkus aort cerrahisi gibi kanama riski daha yüksek kalp cerrahisi geçiren 100 hasta dahil edilmiştir. Çalışma grubu yeni protokol uygulanan ardışık hastalardan oluşmaktadır.(heparin titrasyon protokolü+traneksamik asit) Kontrol grubu ise standart doz heparin (4 mg/kg) uygulanan hastalardan oluşmaktadır.

Her gruptaki 50 hasta (yeni protokol ve standart protokol) uygulanan heparin miktarı, kan-kan ürünü kullanımı, mediastinal drenaj ve reeksplorasyon açısından karşılaştırıldı.

Bulgular: Çalışma grubundaki 50 hastanın 28'i (%56) ilk 24 saat boyunca kırmızı kan hücresi (RBC) transfüzyonu aldı. 3 üniteden fazla RBC transfüzyonu alan hasta sayısı çalışma grubunda daha düşüktü. (%34'e karşı %54; p=0.044). Ayrıca reeksplorasyon oranları benzer olarak bulundu.

Sonuçlar: Sonuç olarak, çalışma sonuçlarımıza göre önerilen heparin titrasyon protokolünün postoperative kanama ve kan ürünü kullanımını azaltmada faydalı olduğu görülmektedir. Kalp cerrahisinde kan transfüzyonu ihtiyacını azaltmak için heparin titrasyon protokolü gibi kan kullanım protokollerinin oluşturulması gerektiğini düşünüyoruz.

Anahtar kelimeler: Kardiyak cerrahi; kan transfüzyonu; drenaj; reoperasyon; heparin; traneksamik asit

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INTRODUCTION

Cardiac surgical interventions are the greatest blood consuming procedures from the point of view of national blood resources [1]. Cardiac surgery remains at the top of the list for blood and blood product utilization among the other surgeries. Blood remains an indispensable product for most cardiac surgical procedures [2]. However, there has developed a tendency to use less blood in our field as well. According to the Society of Thoracic Surgeons Adult Cardiac Surgery Database 2016 Update, blood transfusion rates decreased by 10-15% between 2009 and 2014 [3]. It was documented that the lowest rates occur in mitral valve repair (34.4%) followed by coronary artery bypass grafting (44.5%) [3]. On the other hand, valve replacement, combined (coronary artery bypass grafting + valve) and aortic surgeries, account for at least 50% or higher blood product utilization, for each procedure type [3, 4]. Therefore, strategies to reduce transfusion rates comes into account for this considerable usage of blood [1].

The main reason for reoperation after cardiac surgery is the mediastinal bleeding, which is one of the main complications and accounts for morbidities [5]. Blood and blood product usage after cardiac surgery increases similarly after mediastinal bleeding and subsequent reoperations. It is well-known that blood transfusion is associated with adverse outcomes such as infection, transfusion-related lung injury, transfusion reactions, increased costs and even increased long term mortality [6-8]. All these devastating outcomes should be managed with blood conservation strategies. The main protocol in our institution was changed towards less usage of blood and blood products in the beginning of 2016. Some modifications, such as a heparin titration protocol and routine usage of tranexamic acid infusion for relatively high-risk patients, as aforementioned, were considered for this reason.

We expect that our newly adopted blood conservation strategy may reduce postoperative bleeding and decreases blood and blood product usage. However, there are limited studies regarding the effect of tranexamic acid and heparin titration protocol use on postoperative bleeding in cardiac surgery in literature. Therefore, the aim of this study was to assess the efficacy of heparin titration protocol, along with antifibrinolytics regarding to mediastinal bleeding, re-exploration for bleeding and blood and blood products utilization.

MATERIALS AND METHODS

This study included 100 patients undergoing cardiac surgery with higher risk for bleeding, such as mitral valve replacement, aortic valve replacement and ascending / arcus aortic surgery, between January 2015 and August 2016. Patients undergoing coronary artery bypass grafting, emergency surgery, pediatric patients and those with a history of any hematological disorder prior to surgery, were excluded from the study. This study complies with the Declaration of Helsinki and ethical approval was granted by the local institutional ethical board. (No: 70, Date: 31/10/2016). The data of the patients were obtained from the hospital automation system and patient files.

As of January 2016, use of tranexamic acid, together with the heparin titration protocol described in detail below, has been routinely used in our clinic. The study group consisted of consecutive patients who underwent this protocol. In this heparin titration protocol, an initial 2 mg/kg bolus (half of measured dosage) was administered and afterwards (5 minutes later) ACT was measured. If it was below sufficient levels (< 480 sec), then 1 mg/kg additional heparin (quarter of measured dosage) was administered and repeated if necessary, until adequate ACT levels were achieved prior to cardiopulmonary bypass (Figure 1). Tranexamic acid infusion is routinely used in our clinic along, with the heparin titration protocol. 10 mg/kg/30 min loading dose after induction and 1 mg/kg/hour infusion until the end of operation. 1 mg/kg tranexamic acid is added to the prime solution as well [9]. The control group consisted of patients who were administered a standard dose of heparin (4 mg/kg).

The following data, including patients' characteristics such as age, gender, body weight were analyzed: diabetes mellitus, hypertension, chronic obstructive lung disease, redo surgery, hematological parameters such as hemoglobin, hematocrit, platelet count, active

partial tromboplastin time (aPTT), international normalized ratio (INR), biochemical analysis results such as urea, creatinine, and operative data such as cardiopulmonary bypass (CPB), crossclamp time, measured heparin dosage, initial heparin dosage and additional heparin dosage. Postoperative intensive care unit (ICU) and hospital stay, duration of ventilator-dependency, the amount of drainage and blood and blood product usage as well as mortality, were also recorded.

Anesthetic management and surgical procedures were performed in a standard manner in both groups. In addition, cardiopulmonary bypass techniques (CPB) (including oxygenator and tubing sets – not heparinized) were similar between the groups. In addition, intraoperative and postoperative transfusion thresholds (hematocrit < 24-25%) were kept to avoid unconditional bias.

Statistical Analysis

The data from the study revealed that the reported tranexamic acid may be as effective as the previously used aprotinin and antifibrinolytic agents can reduce blood utilization by approximately 20-25% [10, 11]. We assumed that 30% relative reduction in blood utilization was significant, and therefore the sample size was found to be 41 patients in each group with type-1 error of 0.05 and with 80% power (type-2 error = 0.20). Power analysis was conducted by the G*Power Software 3.1 (Universität Kiel, Germany).

Continuous variables with normal distribution were expressed as mean ± standard deviation, and categorical variables were expressed as number and percentage. Demographic features and perioperative variables were compared by Mann-Whitney U test and chi-square test. Any p value less than 0.05 was considered statistically significant. All statistical analyses were carried out using the SPSS for Windows 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Age, gender, body weight and other demographics were similar between the groups: the demographic data is summarized in Table 1. The standard measured dosage of heparin was similar between the groups (p=0.987). In the study group, eight patients (16%) achieved adequate ACT levels only with the initial dosage (2 mg/kg heparin). Appropriate ACT levels were achieved in 33 patients (66%) in the study group without full dosage of heparinization (Figure 1). Only three patients (6%) in the control group needed an initial dosage of 1 mg/kg heparin after full dosage of heparin administration. Total administered mean heparin dosage just prior initiation of CPB was also higher in the control group (240 mg vs 305 mg; p<0.001). ACT levels at the initiation of CPB was higher in the control group (560 sec vs. 623 sec, p<0.001) (Table 2). In the study group, 89% of the mean standard measured dosage of heparin was sufficient for initiation of CPB (ACT about 560 sec), whereas in the control group 115% of the mean standard measured dosage was administered (ACT about 623 sec) (p<0.001) (Figure 2).

Table 1. Demographic variables of the groups

Preoperative variables	Study group (n=50)	Control group (n=50)	P value
	Mean±SD or n (%)	Mean±SD or n (%)	
Age (years)	53.20±13.40	57.17±12.94	0.179
Male gender	30 (60%)	30 (60%)	1.000
Body weight (kg)	77.28±15.93	77.20±14.37	0.978
Diabetes mellitus	7(14%)	2(4%)	0.162
Hypertension	15 (30%)	18 (36%)	0.347
Chronic obstructive pulmonary disease	9 (18%)	9 (18%)	0.844
Redo surgery	7 (14%)	4 (8%)	0.394
Acetylsalicylic acid	9(18%)	14 (28%)	0.154
Clopidogrel	1 (2%)	0 (0%)	1.000
LMWH	2(4%)	7(14%)	0.082
Preoperative laboratory values			
Hemoglobin (gr/dl)	13.63±1.42	13.32±1.27	0.238
Hematocrit (%)	42.93±4.03	40.91±3.66	0.053
Platelet (x103/uL)	215.42±42.52	226.06±61.45	0.317
Urea (mg/dl)	36.02±13.58	43.40±18.32	0.010
Creatinine (mg/dl)	0.97±0.18	0.99±0.27	0.715
INR	1.31±0.51	1.63±1.03	0.321
aPTT (sec)	35.46±8.01	36.73±8.92	0.394

aPTT: activated partial thromboplastin time; INR: international normalized ratio LMWH: low molecular weight heparin; SD: standard deviation

On the other hand, protamine administration to neutralize heparin was lower in the control group

(251 mg vs. 315 mg; p<0.001), however the protamin:heparin ratio was similar between the groups (p=0.459).

Table 2. Operation types and variables, administered heparin dosage and ACT levels

Variables	Study group (n=50)	Control group (n=50)	P value
	Mean±SD or n (%)	Mean±SD or n (%)	
Operation types			
Mitral valve replacement	10 (20%)	16 (32%)	0.055
Aortic valve replacement	7 (14%)	0 (0%)	
Aortic surgery	8 (16%)	5 (10%)	
Combined aortic surgery	13 (26%)	14 (28%)	
Combined mitral surgery	12 (24%)	14 (28%)	
Operative variables			
Measured heparin dosage (mg)	270.48±55.76	270.18±50.30	0.978
Initial heparin dosage (mg)	171.10±70.29	280.57±64.68	<0.001
ACT after initial dosage (sec)	412.40±108.18	553.55±169.70	<0.001
Additional heparin dosage (mg)	68.50±53.68	24.43±58.94	<0.001
ACT before CPB (sec)	560.74±122.24	622.75±141.51	0.004
CPB period (min)	139.29±52.23	140.67±46.36	0.569
Cross-clamp period (min)	90.76±35.34	96.98±36.93	0.405
Protamine dosage (mg)	251.00±70.34	314.77±57.65	<0.001
Protamine: heparin ratio	1.07±0.12	1.00±0.07	0.459
Need for additional protamine	9 (18%)	13 (26%)	0.334

ACT: activated coagulation time; CPB: cardiopulmonary bypass; SD: standard deviation

The amount of mediastinal drainage was significantly lower in the study group (505 ml vs 651 ml; p=0.047). Mean red blood cell (RBC) utilization for the first 24 hours was 0.46 units for the study group, whereas 0.89 units were used for the control group (p=0.002). Mean fresh frozen plasma (FFP) utilization for the first 24 hours was significantly higher in the control group (1.87 units vs 1.10 units; p<0.001). Total blood product utilization was found to be significantly higher in the control group (4.92 units vs 5.96 units; p=0.013). Relative reduction in RBC utilization for first 24 hours was 16% (from 66% to 56%; p=0.305). On the other hand, relative reduction in FFP utilization was 22% (from 100% to 78%; p<0.001). For further analysis, blood and blood product utilization was categorized as ≥3 units and < 3 units. RBC utilization for ≥3 units was reduced from 54% to 34% with our new protocol (p=0.044). On the other hand, even if it is not significant, there was a relative reduction of FFP utilization (from 86% to 72%; p=0.086).

Table 3. Postoperative variables

Postoperative variables	Study group (n=50)	Control group (n=50)	P value
	Mean±SD or n (%)	Mean±SD or n (%)	
Amount of drainage (ml/first 24 hours)	505.00±311.55	651.09±435.70	0.047
Packed red cells (units/ first 24 hours)	0.46±0.68	0.89±0.80	0.003
Fresh frozen plasma (units/first 24 hours)	1.10±0.93	1.87±0.93	<0.001
Total blood and blood products (units)	4.92±5.19	5.96±4.16	0.013
Reoperation for bleeding	0 (0%)	1 (2%)	1.000
Prolonged ventilation	3 (6%)	7 (14%)	0.182
ICU stay (days)	1.72±2.29	1.30±0.75	0.579
Hospital stays (days)	6.96±3.32	6.98±3.01	0.246
Mortality	2 (4%)	4 (8%)	0.678

ICU: intensive care unit, SD: standard deviation

There was no significant difference regarding to the other outcomes such as ICU and hospital stay, reoperation for bleeding and mortality between the groups.

DISCUSSION

In the present study, heparin titration protocol, along with tranexamic acid, provided less mediastinal bleeding and less utilization of blood for the open-heart surgery. However, the rate of re-exploration for bleeding remained similar. Mediastinal bleeding after cardiac surgery, subsequently necessitating inevitable blood utilization, can be a devastating complication for the patient. Re-exploration for bleeding occurs in about 4-5% at open heart surgery [12]. Afterwards, re-exploration for bleeding subject patients increased the risk of adverse outcomes [13]. It has been considered that the re-exploration plays a major role in the adverse outcomes, however subsequent need for blood utilization has a quite similar influence on

outcomes [5]. Vivacqua et al. reported that either the transfusion or re-exploration for bleeding, similarly and independently contributes to adverse effects including mortality [5]. Blood transfusion is merely associated with several complications [7,14-16]. Transfusion reactions, postoperative infections, pneumonia, cardiac complications, lung injury, etc., are the unfavorable outcomes after blood utilization [14,17,18]. Koch et al. examined the effect of RBC transfusion at open-heart surgery in detail. They reported a significant relation in several morbidities (such as renal failure, prolonged ventilatory support, serious infection cardiac complications and neurological events) and long-term survival with transfusion of RBCs [14, 15]. Engoren et al. reported that blood transfusions in cardiac surgery were associated with increased long-term mortality [7, 16].

As a matter of fact, therefore, implementation of a blood conservation strategy is essential for the cardiac surgery centers. 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Guideline is a beneficial milestone for effective blood conservation methods [1]. Different strategies, ranging from preoperative period to postoperative period including perfusion strategies, are well documented in this guideline. The BART study shows that the lysine analogs are as effective as aprotinin regarding to risk of bleeding and much safer drugs for early mortality [10]. The STS/ACC 2011 guideline strongly recommends tranexamic acid to reduce total blood loss and decrease the number of patients who require blood transfusion [1]. It remains controversial which dose scheme is more beneficial. A complete review of Hodgson shows that low-dose tranexamic acid protocol can be safely given with low seizure risk [9]. At the beginning of 2016, the blood conservation attempts were gradually put into practice. First, low dose tranexamic acid protocol (10 mg/kg bolus + 1 mg/kg/hour infusion + 1 mg/kg priming) was routinely used for high-risk patients for bleeding. Then, the unpublished encouraging results from a study of heparin titration protocol at aortic dissection patients, this protocol came forward for high-risk patient profile. Some heparin dose regimens were recommended at STS/ACC 2007 blood conservation guidelines [1]. Firstly, patient-specific heparin concentrations seemed to be effective for blood utilization, however the major contribution of this system was the stable heparin concentration, especially during prolonged CPB [19]. Secondly, either protamine titration or empiric low-dose heparin regimens to reduce bleeding and blood transfusion requirements, had controversial results [20, 21]. Thirdly, low doses of systemic heparinization (ACT approximately 300 sec) have a risk of under-heparinization and an increased risk of thrombin generation [22]. However, these recommendations are not out of date and still have validity, although they are not included at the current and revised guideline [1]. In the present study, heparin is titrated by serial ACT measurements and therefore under-heparinization, and especially hyper-heparinization, were avoided.

The gold standard for heparin concentrations is the anti-Xa level assessment that is challenging and is not reliable in an operating room setting. On the other hand, the Hepcon system (Hepcon HMS, Medtronic, MN, USA) provides a calculation of individualized heparin dose response curve that is helpful for bleeding and blood conservation protocols. However, the main cumbersome aspect of this device is the occurrence of potential calculation errors, as the device requires estimation of the patient's blood volume and the device measures total heparin, not just antithrombin III-bound functional heparin. Other potential conflicts are inherent inaccuracy of the device and variances at ex vivo heparin activity [23]. Another method for heparin dosing strategy may be the calculation of heparin via lean body weight [24]. However, this approach should, similarly, be developed with regards to large-scale trials. On the basis of these issues, the method described in our study may be an alternative model for heparin dosing strategy. It was obvious that the 89% of the standard measured heparin dosage is sufficient for adequate ACT levels (>480 sec). More precise titration such as repeated one tenths of the dosage instead of quarters may be concluded with much less heparin usage.

Excessive protamine administration may lead to bleeding [25]. The administered protamine in the study group was considerably lower than the control group. At the same time, the protamine:heparin ratio was similar between the groups, indicating

that adequate protamine was administered with regards to administered heparin.

The amount of blood and blood product usage has been generous in our clinic at recent years. However, attempts at blood conservation strategies offer some differences for the blood utilization. The threshold for transfusion has not change much over the years (hematocrit <24-25%). Whereas there has been a tendency to administer FFP widely. New generation surgical teams and intensivists are more restrictive and careful of the issue. Three or more RBC utilization ratios have dropped from 54% to 34% with this new protocol. In the study group, at least one unit of RBC utilization was 56%, which is comparable with the STS reports on outcome [3].

Limitations

The present study has two major limitations. First, this is a pilot study of a newly generated blood conservation strategy for our clinic. Therefore, the patient population for the study is noticeably small, even though the power of the study was 80%. This was also a single center pilot study, and thus the results should not be expanded to other practices or patient population; through additional studies involving a greater number of cases, accurate and definitive results may be produced. Second, this is an observational study and randomizing patients to the technique used was not possible because of different time periods of the patient population.

CONCLUSION

In conclusion, based on our study results, the suggested heparin titration protocol appears to be beneficial for reducing postoperative bleeding and blood product usage. We consider that blood utilization protocols like ours should be established to reduce the need for blood transfusion in cardiac surgery. This may lead to better postoperative outcomes for the patients. However, further large-scale prospective studies are needed to confirm our study results.

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Psychological conditions of patients whose infertility treatment was postponed due to the novel coronavirus pandemic lockdown

Yeni Koronavirüs Salgını Kapanma Süreci Nedeniyle İnfertilite Tedavisi Ertelenen Hastaların Psikolojik Durumları

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ABSTRACT

Aim: In this study, we planned to examine the psychological status of patients who were required to postpone their infertility treatment, by means of an online survey.
Methods: Sixty patients who were in the follow-up were informed and an access link of online survey, which included questions about age, infertility status, Beck's depression inventory(BDI) and Hamilton's anxiety rating scale (HAM-A), were sent to them. Three different grouping systems were used based on (i-) age, (ii-) fertility treatment status and (iii-) indications for assisted reproduction technology treatment.
Results: Mean scores of BDI and HAM-A in the whole group were 39.2(25-67) and 22.1(11-45), respectively. In the evaluation of survey scores according to indications of fertility treatment, BDI scores were between 34.2-44.7 and there was no statistical significance between the groups (p:0.182). HAM-A scores were between 18.7-38.0 and there was no statistical significance between the groups (p:0.185). In addition, there was no statistical significance between groups for BDI and HAM-A (p: 0.962 and 0.423, respectively) according to patients' ART treatment status at the time the 2019-nCoV outbreak began in our country.
Conclusion: Infertile patients will be more prone to depression and anxiety, and it should be noted that potential treatment postponements may increase their depression and anxiety.

Keywords: Coronavirus, Beck's depression inventory, Hamilton anxiety rating scale, infertility

ÖZ

Amaç: Bu çalışmada infertilite tedavisi ertelenen hastaların psikolojik durumlarını online anket aracılığıyla incelemeyi planladık.
Yöntemler: İnfertilite nedeniyle takipte olan 60 hasta anket ile ilgili bilgilendirildi. Yaş, infertilite durumu, Beck depresyon envanteri (BDI) ve Hamilton anksiyete derecelendirme ölçeği (HAM-A) ile ilgili soruları içeren çevrimiçi anketin erişim linki gönderildi. Hastalar (i-) yaş, (ii-) fertilite tedavi durumu ve (iii-) yardımcı üreme teknolojisi (YÜT), tedavisi endikasyonlarına göre üç farklı gruplama sistemi kullanıldı.
Bulgular: Tüm grupta ortalama BDI ve HAM-A skorları sırasıyla 39.2 (25-67) ve 22.1 (11-45) idi. Fertilite tedavisi endikasyonlarına göre anket puanlarının değerlendirilmesinde BDI puanları 34,2-44,7 arasında idi ve gruplar arasında istatistiksel anlamlılık yoktu (p: 0,182). HAM-A skorları 18,7-38,0 arasında idi ve gruplar arasında istatistiksel anlamlılık yoktu (p: 0,185). Ayrıca, 2019-nCoV salgını ülkemizde başladığında hastaların YÜT tedavi durumuna göre BDI ve HAM-A için gruplar arasında istatistiksel olarak anlamlı bir fark yoktu (sırasıyla p: 0.962 ve 0.423).
Sonuçlar: İnfertil hastalar depresyon ve anksiyeteye daha yatkındır ve olası tedavi ertelemelerinin depresyon ve anksiyetelerini artırabileceği unutulmamalıdır.

Anahtar Kelimeler: Koronavirüs, Beck depresyon envanteri, Hamilton anksiyete derecelendirme ölçeği, infertilite

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INTRODUCTION

The 2019 novel coronavirus (2019-nCoV), also known as nCoV or COVID-19 is caused by a new strain of coronavirus (SARS-CoV-2) that was discovered in 2019[1]. The outbreak of COVID-19, which spread rapidly in China and then around the world since it was first seen, was recognized as a pandemic by the World Health Organization (WHO) on March 11 [http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-COVID-19/news/news/2020/3/who-announces-COVID-19-outbreak-a-pandemic]. There are currently more than six million confirmed cases worldwide (data from June 2, 2020) and the numbers are growing rapidly every day.

According to the scientific data, the risks of 2019-nCoV during pregnancy are no greater than the risks that may occur when non-pregnant women acquire this infection [2-3]. However, because the number of cases is very small and the infection is relatively new, the risks that 2019-nCoV will pose to the health of the mother and baby are not yet clear [4-6]. Therefore, there are still many questions about the postponement of new pregnancies during the pandemic period.

While there are many questions about the postponement of new pregnancies, questions have begun to emerge about how to follow a path in infertility treatments during the pandemic period. When contemplating this issue, it was necessary to approach it from a few different angles. During the application of assisted reproductive technologies, if the patient suffered from febrile disease during the embryo transfer period, patient would not have conceived and this might have been also teratogenic [7]. In addition, out-of-town patients were required to travel to the treatment center during the treatment period, and as a result, they were more likely to acquire 2019-nCoV if social distancing and individual hygiene were neglected [8]. Another angle is that immunity might have been affected by the procedures that would be applied to patients during the treatment process, and as a result they might face more serious consequences of a possible infection. In light of all this information, the European Society of Human Reproduction and Embryology (ESHRE) recommended on March 14, 2020 that infertility treatments be postponed: “As a precautionary measure - and in line with the position of other scientific societies in reproductive medicine - we advise that all fertility patients considering or planning treatment, even if they do not meet the diagnostic criteria for 2019-nCoV infection, should avoid becoming pregnant at this time. For those patients already having treatment, we suggest considering deferred pregnancy with oocyte or embryo freezing for later embryo transfer.” [https://www.eshre.eu/Press-Room/ESHRE-News]. On March 17th, 2020, the American Society for Reproductive Medicine (ASRM) published a guidance document on fertility care during the COVID-19 pandemic, calling for suspension of new treatment cycles, cancellation of all embryo transfers and suspension of elective surgeries [https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/COVID-19/COVIDtaskforce.pdf]. As a result of these recommendations, treatments in our center and all over Turkey have been postponed.

After these decision were taken, it was not known how the psychological condition of this group of patients would be affected. Therefore, in this study, we planned to examine the psychological status of patients who experienced a postponed infertility treatment, by means of an online survey.

MATERIAL AND METHOD

This survey study was conducted online at Başkent University Faculty of Medicine, Department of Infertility and Reproductive Endocrinology, between April 19th and 25th, 2020. Patients who were in the follow-up of our Assisted Reproduction Technology (ART) Center were informed about the survey and the access link to the online survey, which included questions about age, infertility status, Beck’s depression inventory (BDI) and the Hamilton anxiety rating scale (HAM-A), were sent to them. Sixty patients completed the survey on a voluntary basis. The study protocol was approved by both the Institutional Ethics Committee and the Ministry of Health and it was performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Beck’s depression inventory contains 21 items on a 4-point scale from 0 to 3 (absent to severe

symptoms). The minimum score is 0 and maximum score is 63. Hamilton's anxiety rating scale consists of 14 items aiming to measure psychic and somatic anxiety on a scale of 0 to 4 (absent to severe), with a total score range 0 to 56. Higher scores indicate greater symptom severity.

Three different grouping system was used based on (i-) age (25-29; 30-34; 35-39; ≥40), (ii-) fertility treatment status (prior failed assisted reproduction technology treatment/treatment was delayed; the preparation of first assisted reproduction technology treatment; prior failed assisted reproduction technology treatment/preparation was delayed; thawed embryo transfer was delayed; treatment began/embryos were thawed) and (iii-) indications for assisted reproduction technology treatment (diminished ovarian reserve; endometrioma and normal ovarian reserve; endometrioma and diminished ovarian reserve; male factor; polycystic ovary syndrome and anovulation; unexplained infertility).

Statistical analyses of the study results were performed using the SPSS v.15.0 (Statistical Package For Social Sciences, Chicago, IL, USA) packaged software. Frequency analyses were performed. The Shapiro-Wilk W test was used to evaluate the distribution of the groups. Since the distribution was not homogeneous for age, IVF indication and status of IVF, the Games-Howell post hoc test was used to evaluate the differences between the groups in a One-Way ANOVA analysis. A P value of < 0.05 was considered statistically significant.

RESULTS

The study included sixty patients. The number of patients under 35 and ≥35 years old were 37 (61.7%) and 23 (38.3%), respectively. The mean scores of BDI and HAM-A in the entire group were 39.2 (25-67) and 22.1 (11-45), respectively.

In the evaluation of the survey scores with regard to age, there was no statistical significance between groups for BDI and HAM-A (p: 0.778 and 0.993, respectively). Mean BDI scores were between 37.0-40.5 and the highest score was in the ≥40 years old age group. HAM-A scores were very similar between all groups with a range of 20.0-22.4.

The most frequent indications of ART treatment were diminished ovarian reserve (DOR), endometrioma with normal ovarian reserve (NOR) and endometrioma concomitant with DOR, with a distribution of 20 (32.8%), 14 (23.0%) and 13 (21.3%), respectively. BDI scores were in the range of 34.2-44.7 and there was no statistical significance between the groups (p:0.182). HAM-A scores were in the range of 18.7-38.0 and there was no statistical significance between the groups (p:0.185). The results of surveys according to indications of fertility treatment were shown in Table 1.

Table 1. Beck's depression inventory (BDI) and Hamilton anxiety rating scale (HAM-A) according to indications for assisted reproduction technology treatment

Assisted Reproductive Technologies treatment indication	n	BDI Score	P	Hamilton Score	P
DOR	20	38.5±8.4		21.5±6.7	
Endometrioma and NOR	14	39.0 ±11.8		22.6±8.6	
Endometrioma and DOR	13	44.7±7.2	0.182	22.6±6.4	0.185
Male factor	9	34.2±6.6		0.182	
PCOS/anovulation	3	38.3±9.8		25.0±7.8	
Unexplained infertility	1	36.0		38.0	

DOR: Diminished ovarian reserve, NOR: Normal ovarian reserve, PCOS: Polycystic ovary syndrome, BDI: Beck's depression inventory

Table 2 shows survey results according to patients' ART treatment status when the 2019-nCoV outbreak began in our country. There was no statistical significance between groups for BDI and HAM-A (p: 0.962 and 0.423, respectively). Mean BDI scores were between 38.4-41.3 and the highest BDI score was in the patients who had prior ART history and at the evaluation phase for the next IVF treatment. HAM-A score was also highest in the same group (25.0).

DISCUSSION

In this study, we aimed to assess the psychological status of patients who experienced a postponement of their infertility treatment. Although we did not find any statistical difference in BDI and HAM-a scores among the groups, we found that BDI and HAM-a scores of all infertile patients were higher than the previous studies conducted in our infertility center and the other center in Turkey [9-11] (Table 3).

Table 2. Beck's depression inventory (BDI) and Hamilton anxiety rating scale (HAM-A) according to fertility treatment status at the beginning of 2019 Novel Coronavirus Pandemic

Status of fertility treatment at the beginning of 2019 Novel Coronavirus pandemic	n	BDI Score	p	Hamilton Score	p
Prior failed assisted reproduction technology treatment/ Treatment was delayed	19	38.6±7.5		22.4±6.3	
The preparation of first assisted reproduction technology treatment	14	39.2±10.7		20.6±7.4	
Prior failed assisted reproduction technology treatment/ Preparation was delayed	10	41.3±4.7	0.962	25.0±6.8	0.423
Thawed embryo transfer was delayed	10	39.2±11.2		19.4±6.6	
Treatment began/Embryos were thawed	7	38.4±13.4		23.7±10.1	

ET: Embryo transfer, BDI: Beck's depression inventory

Table 3. BDI scores in Turkish women – A comparison with before 2019 Novel Coronaviruspandemic [10-12]

Study	Study Design	Study Cohort	Study aim	BDI Score		Conclusion
				Infertile women	Fertile women	
Ozturk et al. (2019)	Cross sectional and comparative study	Infertile women vs fertile women	Compare to depression and anxiety level of Turkish infertile and fertile women	11.5 ± 9.7	9.9 ± 9.0	The BDI total scores did not significantly differ
Pinar et al. (2012)	Cross sectional study	Infertile couple vs fertile women	Compare to depression and anxiety level of Turkish infertile and fertile women	25.00± 11.58	19.87 ± 9.78	a higher prevalence of depression and anxiety in the infertile group
Erdem et al. (2014)	Descriptive and sectional study	Turkish infertile women	Determine the relationship between perceived social support and depression in infertile women	12.55 ± 8.07		Symptoms of depression decreased as the women's perceived social support increased.
Current study	Online survey study	Turkish infertile women patients who are postponed of treatment	Examine the psychological status of patients who are postponed of infertility treatment due to pandemic	39.2 ± 9.19		Possible treatment postponements may increase their depression

BDI: Beck's depression inventory

Infertility is a major predicament that may cause stress in human life [12,13]. In the literature, there have been many studies examining the association between depression / anxiety and infertility, and these studies have shown that infertile women had higher scores on the depression and anxiety scales than those the control group [11,14,15]. It has been reported that there are several risk factors which may cause depression in infertile patients, including female gender, repeated treatment cycles, unsuccessful treatments, a low socioeconomic state, lack of a partner's support for women, previous depression, and the long duration of infertility [14,16,17] and even patients may apply experimental treatment approaches [18]. As a result, infertility and treatment process of these patients are considered as a cumulative trauma. Therefore, any disruption of the treatment, for any reason, including financial problems, loss of hope as a result of unsuccessful treatment, lack of response during treatment that may occur in the treatment processes, may be an additional source of stress. In addition to these factors, the postponement of infertility treatments and a nationwide lockdown caused fear, anxiety and loss of hope in the patients, as we were made aware of through messages and telephone calls received from the patients. Therefore, we planned this study to measure the depression and anxiety of these patients in this process and applied the BDI and HAM-a to patients who agreed to be involved in the study. As a result, we found higher scores in BDI and HAM-a, in patients included in this study, than those reported in infertile patients in the literature [9-11] (Table 3).

CONCLUSION

Infertile patients go through a stressful period in their treatment process. Therefore, when planning treatments for these patients, it should be kept in mind that they will have an increased propensity for depression and anxiety, and it should be noted that potential treatment postponements may increase their depression and anxiety. Remaining connected with patients through the use of text messages, live broadcasts and online video messaging may encourage and direct the patients to adapt to these challenging times.

Limitations

The present study had some limitations, including a low number of patients, lack of control groups and lack of depression and anxiety scores of patients prior and after the pandemic, which is ongoing. However, considering that this pandemic process was an extraordinary event, it was problematic to obtain BDI and HAM-A scores before and after the pandemic, as the survey was performed at the time of the lockdown. Therefore, we compared the scores we obtained in our study with previous studies in infertile patients in the literature. Despite these limitations, this is to the best of our knowledge, the first and only study on this topic.

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Clinical outcomes of laparoscopic treatment of non-palpable testis in children at a tertiary pediatric surgery center

Üçüncü basamak bir çocuk cerrahisi merkezinde çocuklarda palpe edilemeyen testislerin laparoskopik tedavisinin klinik sonuçları

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ABSTRACT

Aim: Non-palpable testis is defined as the absence of the testis in the inguinal canal and scrotum in a male patient. It is important to define the condition and location of the non-palpable testis, to prevent the risks of infertility and malignant transformation of the testis in patients. We aimed to evaluate the results of the laparoscopic approach we applied in the treatment of pediatric patients with non-palpable testes.

Methods: Patients with non-palpable testes, diagnosed and treated by the laparoscopic approach in a tertiary pediatric surgery center, were evaluated retrospectively. In the treatment protocol, laparoscopic abdominal exploration, two-stage Fowler-Stephens laparoscopic orchiopexy, primary laparoscopic orchiopexy and inguinal exploration surgical approaches were applied according to the case characteristics

Results: Data from 54 testes in 45 pediatric patients were evaluated. Intra-abdominal testis was detected in 46.2% of the cases, with 88% of them at the entrance of the internal inguinal ring. After laparoscopic abdominal exploration, two-stage Fowler-Stephens in 7 (28%), primary laparoscopic orchiopexy in 18 (72%) were applied of testes. Inguinal exploration was performed in 27 (50%) whom no testis could not found. Seventeen (73.9%) of 23 testes that were descended into the scrotum remained viable, while atrophy occurred in 6 (26%) of them. Viable testis cells were not detected in the histopathology of 27 excised nubbins.

Conclusions: The laparoscopic approach is a reliable and effective method in the diagnosis and treatment of non-palpable testis. Localization of intra-abdominal testes may support consideration of the inguinal exploration approach as the primary surgical intervention.

Keywords: Testis; undescended testis; laparoscopy; orchiopexy; pediatrics

ÖZ

Amaç: Palpe edilemeyen testis, erkek bir hastada testisin inguinal kanal ve skrotum içerisinde bulunmaması şeklinde tanımlanır. Hastada infertilite ve testiste malign transformasyon gelişim riskini engellemek için palpe edilemeyen testisin yerleşimi ve durumunun tanımlanması önemlidir. Amacımız, palpe edilemeyen testis tanılı çocuk hastalarda tedavide uyguladığımız laparoskopik yaklaşımın sonuçlarını değerlendirmekti.

Yöntemler: Üçüncü basamak bir çocuk cerrahisi merkezinde palpe edilemeyen testis tanısı konulmuş ve laparoskopik yaklaşım ile tedavi edilmiş hastalar geriye dönük olarak incelendi. Hastaların özelliklerine göre tedavi protokolünde, laparoskopik abdominal eksplorasyon, iki aşamalı Fowler-Stephens laparoskopik orşiopeksi, primer laparoskopik orşiopeksi ve inguinal eksplorasyon uygulandı.

Bulgular: Kırk beş çocuk hastadaki 54 testise ait veriler incelendi. Vakaların %46.2'sinde intra abdominal yerleşimli saptanan testislerin %88'i internal inguinal ring girişinde yerleşimliydi. Laparoskopik abdominal eksplorasyondan sonra testislerin 7 (%28)'sine iki aşamalı Fowler-Stephens, 18 (%72)'ine primer laparoskopik orşiopeksi uygulandı. Testis bulunamayan 27 (%50) vakaya inguinal eksplorasyon uygulandı. Skrotuma indirilen 23 testisin 17 (%73.9)'si normal iken, 6 (%26)'sında atrofi gelişti. Eksize edilen 27 inguinal nubbinde testis ait canlı hücreler saptanmadı.

Sonuçlar: Palpe edilemeyen testisin tanı konulması ve tedavisinde laparaskopi güvenilir ve etkili bir yöntemdir. Abdomen içi testislerin yerleşim yeri, öncelikli cerrahi yaklaşım olarak inguinal eksplorasyonun düşünülmesini destekleyebilir.

Anahtar Kelimeler: Testis; inmemiş testis; laparoskopi; orşiopeksi; pediatri

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INTRODUCTION

Non-palpable testis (NPT) is the absence of the testis in the scrotum and inguinal canal. Cases of non-palpable testis constitute 20-30% of the undescended testis cases [1]. Because of the low fertility in patients with undescended testis and the increased incidence of carcinoma in situ in the affected testes, it is important to determine the location and developmental status of a non-palpable testis [2, 3].

Physical examination and radiological imaging methods are used to locate a NPT in the inguinal and scrotal regions. However, the American Urology Association (AUA) has emphasized that the location of the testis cannot be detected 100% through pre-operative imaging methods. AUA does not recommend ultrasound examination because the sensitivity and specificity of ultrasound about NPT detection, which is the most frequently performed examination, is low (45 and 78% respectively) [4]. Patients with bilateral NPT should be evaluated for Disorder of Sex Development (DSD) [5].

Although there are different options such as laparoscopic exploration of the abdomen or inguinal exploration to determine the location of the testis in patients with non-palpable testis, it is a common and accepted practice to start with a laparoscopic exploration [6, 7]. In patients without an intra-abdominal testis, atrophied testicular tissue (nubbin) may be present in the inguinal canal or scrotum. Germ cells have been identified in the histopathology of 0-16% of inguinal/scrotal nubbins, and routine excision of the nubbin is a controversial issue [8].

The treatment goal for an abdominally-located testis is to bring it into the scrotum in a viable and tension-free condition. Primary orchiopexy and one- or two-stage Fowler-Stephens surgeries are the main surgical methods to achieve this aim [4]. These surgical approaches can be performed through open surgery or laparoscopic methods.

In our study, it was aimed to evaluate the results of the laparoscopic approach we applied in the treatment of pediatric patients with NPT.

METHODS

Between January 2007 and January 2020, a diagnosis of NPT was made in our clinic, the laparoscopic method was used in the treatment, and pediatric patients under 18 years were investigated. The study was approved by the Çukurova University Faculty of Medicine Ethics Committee (Meeting no: 109, Decision no: 4). The medical records of the patients regarding diagnosis, treatment and follow-up were evaluated retrospectively. Informed consent was obtained from the families of the patients involved in the study. Patients who did not have a palpable testis in the inguinal and scrotal region on physical examination were accepted with a diagnosis of a non-palpable testis. For these patients, ultrasound was performed to detect the presence of gonad in their inguinal and scrotal regions.

In the surgical approach in patients with non-palpable testis, the presence of normal or atrophic testicular tissue was checked by examining the inguinal canal and scrotum after induction of general anesthesia. Laparoscopic exploration was initiated when there was no structure compatible with the testis. The abdomen was entered into from the umbilicus with an open method with a 5 mm trocar. Pneumoperitoneum was created with CO2 gas at a pressure of 10-12 mmHg. Testis, ductus deferens, vessels and structures entering the inguinal canal were evaluated. If such evaluation with the camera view was not sufficient, a 5 mm trocar was placed just below the umbilicus level, just lateral to the rectus muscle on the right or left, using the open method. In case it was decided to perform primary laparoscopic orchiopexy or Fowler-Stephens surgery, the second 5 mm trocar was placed symmetrical to the first trocar. After the intra-abdominal testis was released, the ductus deferens and vessels were preserved, and the testis was made to descend into the scrotum by creating a new pathway through the inguinal canal. The testis was fixed by trying to make it descend into the scrotum without tension. Two-stage Fowler-Stephens surgery was performed in patients with short intra-abdominal testicular vessels and where it was considered that the testis could not be made to descend into the scrotum.

In the first stage of Fowler-Stephens, the

connection between the testis and the testicular vessels is separated and blood supply of the testis is provided from the collaterals. At least 6 months after the first session, the testis, which was planned to descend, was released while maintaining the peripheral blood flow. Inguinal exploration was performed in cases where intra-abdominal testis was not detected through laparoscopic exploration. Atrophic tissues that could be testis in the inguinal canal or scrotum were excised. Treatment success was defined as the testis being into the scrotum and being alive in the scrotum at follow-up.

Statistical analysis: IBM SPSS Statistics Version 20.0 program was used for data analysis. Age at diagnosis, age at surgery and duration of follow-up were defined as the median value (minimum-maximum), and other quantitative data as percentages.

RESULTS

The data of 54 non-palpable testes in 45 patients who met the research criteria were analyzed. The demographic characteristics and comorbidities of the patients with a median age of diagnosis of 12 (2-144) months are shown in Table 1.

Table 1: Characteristics of Study Group

Age of diagnosis (month) (n=45)	12 (2-144)
Age of surgery (month) (n=45)	24 (6-156)
Concomitant diseases n (%) (n=45)	12 (26.6)
Patent ductus arteriosus	2
Meningomyelosel	1
Hepatoblastoma	1
Russel Silver syndrome	1
Prune Belly syndrome	1
Posterior uretral valve	1
Tricuspit stenosis	1
Prader Willi syndrome	1
Malign mesenchimal tumor	1
Aort stenosis	1
VACTERL	1
Side (n=45)	
Right	13 (28,8)
Left	23 (51.1)
Bilateral	9 (20)
Follow-up (PLO+ FS2) (month) (n=17 testes)	12 (4-130)

Data are given as number of cases (n), percentage (%) and median (minimum-maximum), PLO: Primary laparoscopic orchiopexy, FS2: Fowler-Stephens stage 2

During the diagnosis, physical examination and ultrasound findings of the scrotal and inguinal regions were used. Nine patients with bilateral NPT were evaluated by the pediatric endocrinology department, with karyotype analysis and human Chorionic Gonadotrophin (hCG) stimulation test performed. The karyotype of these 9 patients was determined as 46 XY, and 8 patients had a testosterone response to hormone stimulation. Laparoscopic abdominal exploration was performed for all the patients as the primary surgical method. The treatment management of patients with non-palpable testis is presented in Figure 1. Inguinal exploration was performed in one of three patients whose intra-abdominal testis was not detected in the laparoscopic exploration, whose testicular artery was not developed, and who ended up blind. Laparoscopic exploration findings and data about histopathology and complications are depicted in Table 2. As a result of the treatment, 23 (92%) of 25 intra-abdominal testes found in NPT patients descended to the scrotum. In their follow-up, 17 (73.9%) of these 23 testes were viable. After primary laparoscopic orchiopexy, a 30% reduction in testis size was detected in one patient, the blood supply to which was found to be normal in the follow-up. The outcomes of surgical procedures presented in Table 3.

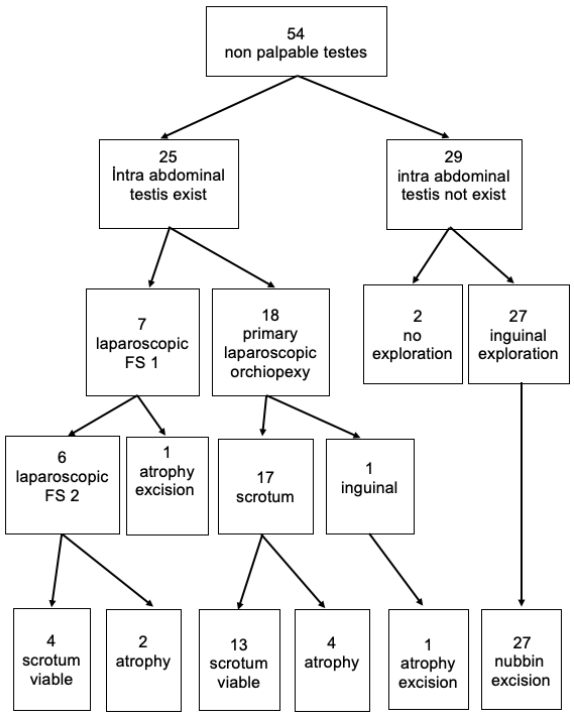

Figure 1. Treatment management of patients

Table 2: Data of The Laparoscopic Exploration, Histopathology and Complication

	n	%
Intra-abdominal testis	54	
-Yes	25	46.2
-Non	29	53.8
Localization of intra-abdominal testis	25	
-Not at the entrance of the internal inguinal ring	3	12
-At the entrance of the internal inguinal ring	22	88
Appearance of testicular artery in the abdomen (Intraabdominal testis (-) group)	29	
-Normal	17	58.6
-Atrophic	9	31
-Blind ending	3	10.3
Histopathology (nubbin)	27	
-Testis tissue	0	0
-Ductus Deferens	16	59.2
-Calcified and fibrous tissue	11	40.8
Complication	25*	32
-Testis atrophy	8	

Data are given as number of cases (n) and percentage (%). *: Patients with intra-abdominal testis detected

Table 3: Successful rate of surgical interventions

	n	Success n (%)
Primary laparoscopic orchiopexy	18	13 (72.2)
Two-stage Fowler-Stephens laparoscopic orchiopexy	7	4 (57.1)
Testis that final position is in the scrotum and viable (testis that orchiopexy performed)	23	17 (73.9)

Data are given as number of cases (n) and percentage (%).

DISCUSSION

Our study aimed to evaluate the results of the laparoscopic approach in the treatment of patients with NPT. According to our clinical results, the success of the FS approach and primary laparoscopic orchiopexy seems low, compared to the literature. In our study group, the location of the testes in the abdomen was mostly close to the entrance of the internal inguinal canal, suggesting that it may be appropriate to start the surgery with inguinal exploration first.

The median age of diagnosis of the patients was 12 (2-144) months, and the median age of surgery 24 (6-156) months. Although the median age at diagnosis was consistent with previous publications, the median age at surgery was found to be higher [9,10]. Of the patients, 51.1% had NPT on the left side, 28.8% on the right, and 20% had bilateral NPT. Detection of non-palpable testis mostly on the left and the frequency of bilateral NPT were consistent with the literature [9,10,11,12].

Tasian et al. reported that the sensitivity of ultrasound in showing the testis in NPT patients was 45%, that it could not reliably localize the testis and could not exclude the presence of intra-abdominal testis [4]. The American Urology Association does not recommend the use of diagnostic radiological imaging in patients with NPT, due to the low reliability of ultrasound, the danger of ionizing radiation in computed tomography, the need for anesthesia in children during magnetic resonance imaging (MRI), and the cost of MRI [5]. The European Association of Urology / European Society for Paediatric Urology (EAU/ESPU) considers it appropriate to use methods such as ultrasound and MRI only in cases of suspected DSD and in special cases where it is important to measure palpable testis size [13]. All patients in our study group were evaluated by ultrasound. No testis or nubbin tissue could be demonstrated in the inguinal region and scrotum on the non-palpable side of the testis in any patient.

As stated in the guidelines of AUA and ESPU, karyotype research and hCG stimulation test were performed to evaluate the risk of DSD in patients with bilateral NPT [5,13]. There was no testosterone response to the hCG stimulation test in a patient with bilateral NPT who did not have an intra-abdominal testis and had a karyotype of 46 XY. In the inguinal exploration of this patient, no tissue compatible with the testis was observed on the left, while the removal of 5 mm tissue with streak gonad appearance on the right was not accepted by the family. There was a testosterone response to the hCG hormone in other patients with bilateral NPT. In patients with non-palpable testis, if the testis is not palpable in the physical examination performed under anesthesia, abdominal exploration with a laparoscopic approach is widely accepted to evaluate the presence of intra-abdominal testis [6]. In all our patients, laparoscopic abdominal exploration was performed first when the testis was not palpable under anesthesia. Intra-abdominal testis frequency in NPT patients has been defined as 40-

61% in some studies [9,12,14,15]. In our study, 25 (46.2%) of the 54 NPTs were found to have testis in the abdomen. When the locations of 25 intra-abdominal testes were evaluated, 22 (88%) were found to be at the entrance of the internal inguinal ring. There are different opinions about starting the primary surgical approach with inguinal/ scrotal exploration or laparoscopic exploration of the abdomen in NPTs [7]. Igarashi et al. reported that the testis was found and descended into the scrotum by inguinal exploration in 39% of 72 patients with NPT in the operations they started with inguinal exploration, and they recommended that laparoscopy be done after the inguinal approach [9]. Callewaert et al. reported that the testes could be made to descend into the scrotum with the high scrotal Bianchi incision in 78% of 46 NPTs [7]. The fact that the intra-abdominal testes in our study were close to the internal inguinal ring entrance in a large proportion of 88%, evaluated together with the literature, makes it reasonable to re-question the place of laparoscopy in the primary surgical approach.

The term 'high testis' defines a testis that cannot be made to descend into the scrotum without tension, due to the shortness of the ductus deferens and testicular artery [16]. Methods such as the Shehata technique, gradual orchiopexy by preserving the spermatic vessels, autotransplantation, and the application of the 1- or 2-stage FS technique have been described for these testes [17,18,19,20,21]. AUA and EAU/ESPU recommend 1- or 2-stage FS orchiopexy for the treatment of high intra-abdominal testis [13, 19]. It has been reported in different publications that the two-stage approach has better success rates than the single-stage approach (85%, 80%, respectively) [16,19]. Esposito et al. revealed a success rate of 83.3% in 12 patients who were followed up for more than 10 years with two-stage FS and found a loss of size in the testes which descended into the scrotum, compared to the normal testis on the opposite side [22].

Primary orchiopexy could not be performed in 7 (28%) of the 25 intra-abdominal testes due to testicular artery shortness, and these patients underwent FS surgery spread over 2 sessions. Post-first stage atrophy developed in one of the 7 testes in which two-stage FS was applied and this testis was excised laparoscopically. The remaining 6 testes were reduced to the scrotum with FS 2 stage surgery. In the follow-up of these testes, testicular atrophy developed in 2 patients. The development of the remaining 4 testes was normal. Our success rate in the two-stage FS approach is 57.1%, which is below the literature. This may be due to the low number of patients and the failure to preserve the blood supply to the testis during FS 2, the insufficient blood supply to the testis after FS 1, or making the testis descend tensely into the scrotum, which may disrupt the blood supply.

Primary laparoscopic orchiopexy was applied to 18 (72%) of the 25 intra-abdominal testes in the study group. While 17 testes descended into the scrotum with the help of laparoscopy, one testis was fixed in the middle of the inguinal canal, where it could be brought distally. However, during the follow-up, atrophy developed in this testis and it was excised. Thirteen (72.2%) of the 18 testes that underwent primary laparoscopic orchiopexy were viable in the scrotum. This success rate can be termed low compared to 96.4% in the literature [23]. Of the 23 testes (6 FS 2nd session, 17 primary laparoscopic orchiopexy) that descended into the scrotum, 17 (73.9%) were found to be in the scrotum and were found viable by doppler ultrasound examination. In 6 of the 23 testes, reduction in testis size was detected in the first 3 months post-operatively, and their size decreased below 0,5 cm in the follow-up. One of these three atrophic testes was excised.

An important evaluation step in patients without testis in intra-abdominal exploration is the evaluation of the testicular artery. The AUA and EAU/ESPU guidelines recommend inguinal exploration if the testicular vessels appear to have entered the inguinal canal, while further processing is not recommended in the presence of a vessel with a blind-ending [15, 19]. However, Sturm et al. reported that inguinal/scrotal nubbin was present in 72% of 36 cases whose testicular vessels ended blindly in laparoscopic exploration [15].

Excision of nubbin tissue, if present, is the approach generally used in inguinal or scrotal exploration. The necessity of removing the nubbin, which is

thought to be atrophic testicular tissue, is due to the concern that malignant transformation may occur in the tissue [24]. Natajara et al. reported that viable germ cells and seminiferous tubules are found in 1 in 10 and 1 in 20, respectively, in inguinal/scrotal nubbins [8]. Some researchers differ and argue that the risk of malignancy development from nubbin tissues is very low and that the defined samples are not strong, thus finding is no strong evidence for routine nubbin excision [8,25]. In our study, it was observed that the testicular vessels ended blindly before entering the inguinal canal in 3 of the cases where no intra-abdominal testis was detected. Inguinal exploration was performed in one of these 3 cases and 4 mm of nubbin tissue was excised. Histopathological examination of this tissue has been reported as ductus deferens and epididymis. Inguinal exploration was not performed for the other two testes. Histopathological examination of 27 nubbin tissues, which were excised, was reported as ductus deferens in 16 (59.2%) and calcified and fibrous tissue in 11 (40.8%); viable testis structures were not detected in these tissues.

The most common complication in the study group was atrophy of 8 (32%) of the 25 testes with intra-abdominal presence during the treatment process. Testis ascent and surgical site infection were not detected in any of the patients. The follow-up period of 17 testes that descended into the scrotum after orchiopexy was 12 (4-130) months. After weekly, monthly, 3-month, and 6-month follow-ups after orchiopexy, annual physical examination and testis dimensions were followed by scrotal ultrasound.

There are some important limitations in our study. The limited number of patients participating in the study makes it difficult to properly evaluate the results of an infrequent surgical method such as FS. A standard and homogeneous approach in the treatment of NPT may not have been developed due to the study not being designed prospectively, the cases being performed by different surgeons, and the effects of inexperienced surgeons receiving training.

CONCLUSIONS

The laparoscopic approach is a reliable and effective method in the diagnosis and treatment of non-palpable testis. Our study showed inguinal exploration as a suitable alternative to laparoscopic exploration for primary surgical intervention, to detect the presence of testis in NPT and treatment, since intra-abdominal testes were most likely detected at the entrance of the inguinal canal. Further research is essential to reveal the causes of testicular atrophy after orchiopexy.

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RESEARCH ARTICLE

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Endoscopic findings of the gastrointestinal tract and conjunctions with preceding tomography findings

Gastrointestinal sistemin endoskopik bulguları ve tomografi bulguları ile ilişkisi

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ABSTRACT

Aim: Abdominopelvic computed tomography is commonly used for delineating the causes of abdominal pain. While its popularity has increased, the rate of non-specific findings like gastrointestinal wall thickening has also increased. We aimed to determine whether a CT finding of thickened wall predicted a pathological finding on subsequent endoscopic evaluation.

Method: This retrospective study was conducted on adult patients who underwent endoscopic or colonoscopic evaluation at our center in 2019 and had a preceding abdominopelvic CT within a month before this investigation. Patients' gastric or colonic wall thicknesses were measured during CT scans. Endoscopy or colonoscopy results of these patients were retrieved, and their correlation with wall thicknesses was analyzed.

Results: The study cohort included 647 patients. While 106 (16.38%) underwent endoscopy, 541 (83.62%) underwent colonoscopy. The endoscopic biopsies were malignant in 101 patients (95,3%) and benign in 5 (4,7%) patients. The CT sections showed thickened wall in 93 (87.7%) patients. Comparison of the patients with and without a thickened wall revealed no difference concerning malignancy rates. Increased colonic wall thickness was detected in 506 (93,5%) of the CT sections. Normal or benign colonoscopic biopsy findings were reported in 19 (3,5%) patients. Adenocarcinoma was detected in 456 (84,2%) patients. Comparison of the patient groups with or without wall thickening did not reveal any significant differences regarding malignancy rates.

Conclusion: Endoscopic-colonoscopic evaluations should be performed in patients with gastrointestinal wall thickening in CT scans since the diagnostic and predictive accuracy are limited when a single test like CT is used.

Keywords: Endoscopy, Colonoscopy, Wall thickening, Abdominal Computed Tomography

ÖZ

Amaç: Abdominopelvik bilgisayarlı tomografi, karın ağrısı nedenlerini belirlemek için yaygın olarak kullanılmaktadır. Tomografinin popülaritesi artarken gastrointestinal duvar kalınlaşması gibi nonspesifik bulguların oranı da artmıştır. Duvar kalınlığı artışının, endoskopik değerlendirmede patolojik bir bulguyu tahmin edip etmediğini belirlemeyi amaçladık.

Yöntemler: Bu retrospektif çalışma, 2019 yılında merkezimizde endoskopik veya kolonoskopik değerlendirme yapılan ve bu incelemeden önceki bir ay içinde abdominopelvik tomografi yapılan erişkin hastalar üzerinde yapılmıştır. Tomografi taramaları sırasında hastaların mide veya kolon duvar kalınlıkları ölçüldü. Bu hastaların endoskopi veya kolonoskopi sonuçları alınarak duvar kalınlıkları ile korelasyonları incelenmiştir.

Bulgular: Çalışma 647 hastayı içeriyordu. 106'sına (%16.38) endoskopi yapılırken, 541'ine (%83.62) kolonoskopi yapıldı. Endoskopik biyopsiler 101 hastada (%95,3) malign, 5 (%4,7) hastada benign idi. BT kesitlerinde 93 (%87.7) hastada kalınlaşmış duvar görüldü. Duvar kalınlık artışı olan ve olmayan hastaların karşılaştırılması, malignite oranları açısından farklılık göstermedi.BT kesitlerinin 506'sında (%93,5) kolon duvar kalınlığında artış saptandı. 19 (%3,5) hastada normal veya benign kolonoskopik biyopsi bulguları rapor edildi. 456 (%84,2) hastada adenokarsinom tespit edildi. Duvar kalınlık artışı olan ve olmayan hasta gruplarının karşılaştırılması malignite oranları açısından anlamlı bir farklılık ortaya koymadı.

Sonuçlar: Tomografi gibi tek bir test kullanıldığında tanısal ve prediktif doğruluk sınırlı olduğundan tomografi taramalarında gastrointestinal duvar kalınlaşması olan hastalarda endoskopik-kolonoskopik değerlendirmelerİ de ek olarak yapılmalıdır.

Anahtar Kelimeler: Endoskopi, Kolonoskopi, Duvar Kalınlığı, Bilgisayarlı Tomografi

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INTRODUCTION

Computed tomography (CT) has become a common imaging technique for delineating the causes of abdominal pain. Its popularity has increased as a result of its advanced proficiency, improved resolution and image precision [1]. Conjointly, the rate of non-specific findings has also increased with the frequent use of CT. These non-specific findings are sometimes difficult to interpret by clinicians [2]. One of these findings is the visceral wall thickening, either at the upper or lower gastrointestinal tract. While some incidental reports of wall thickening may represent normal findings, some minor changes could be an early sign of malignancy [3, 4].

In this era of frequent CT imaging, it is common to be faced with such dilemmas and the soundest way to resolve this problem is to perform endoscopic and colonoscopic evaluations, where the entire gastrointestinal tract can be screened and biopsied if necessary [5]. However, this approach is not feasible for a number of patient groups, namely the elderly with their multiple comorbidities and high frailty scores [6]. Invasive interventions can lead to high procedure-related complications and poor outcomes in this group [7, 8]. On the other hand, an endoscopic evaluation for young and healthy patients may have a low yield for delineation of gastrointestinal wall thickening detected in CT.

Several clinical trials have attempted to solve this dilemma by investigating the correlation of wall thickness observed in CT scans with those patients' endoscopic findings [9-12]. However, this approach might have led to a selection bias: in these patients, the clinician may have been prompted to perform an endoscopic evaluation in which he sought to find a pathological explanation to the CT findings. To prevent a potential selection bias, we considered a different approach in our study. We reviewed all the patients who underwent endoscopic or colonoscopic evaluations at our general surgery clinic. Subsequently, we reviewed our institution's CT image repository to see if these patients had a preceding CT performed within one month. Thus, we were able to form a study cohort consisting of symptomatic patients, who presented with a wide range of gastrointestinal symptoms, representing the actual patient population encountered at general surgery and gastroenterology clinics. We sought to determine whether a CT finding of thickened gastrointestinal wall predicted a pathological finding on subsequent endoscopic evaluations, through the analysis of this population.

MATERIALS AND METHODS

Study Population

This study was designed as a retrospective clinical study performed on adult patients who underwent endoscopic or colonoscopic evaluation of the gastrointestinal tract and had a preceding computed tomography of the abdomen within a month prior to this investigation. The study was conducted between January 2019 and December 2019 in Diskapi Training and Research Hospital, Department of General Surgery. It was approved by the Ethical Review Committee of the same hospital (12.11.2018, 56/12). All flexible endoscopy or colonoscopy procedures were performed using a Fujinon® Japan, 2008, EC 450 HL5 Colonoscopy device and Fujinon 2009 EG 250PE5 Gastroscopy device, by surgeons with at least 5 years of experience in colonoscopy and endoscopy, and biopsies were taken from suspicious areas or areas with overt disease. In cases where no overt disease or suspicious areas were observed, random biopsies were taken according to our institutional protocol.

Patients with insufficient bowel cleansing or a suboptimal colonoscopy were excluded based on previously dictated colonoscopy reports (i.e., patients necessitating re-evaluation). All patients included in the study cohort had a helical CT with intravenous contrast medium (Omnipaque®; OPAKIM Medical Products Industry and Trade Inc., Istanbul, Turkey), and all CT scans were performed with a slice thickness of 5-mm. Patients without a preceding intravenous contrast CT scan, those who had inadequate distension of the gastrointestinal tract, patients who had systemic diseases such as chronic kidney failure or heart failure, and those patients under the age of eighteen were all omitted. Additionally, patients with a history of previous abdominal surgery or patients with a known gastrointestinal disease were also omitted. Abdominal CT sections of the patients were re-evaluated by radiologists with

at least 5 years of experience, blinded to the endoscopic evaluations of those patients.

Gastrointestinal wall thicknesses on the CT sections were measured individually, and a width of 0-5 mm was considered normal, whereas a width of more than 5 mm was considered "increased wall thickness". Patients were classified into two main groups according to the presence of colonic wall thickening. These two groups were analyzed and compared regarding patient characteristics and histopathology results. For further analysis, CT findings were classified according to the grade of segmental wall thickening: while 0-5 mm was considered standard thickness, 5-20 mm was defined as moderately increased, and 20-60 mm was considered severely increased thickness (Figures 1 and 2). Patients with diffuse wall thickening were also identified. Patients were analyzed separately in endoscopy and colonoscopy groups.

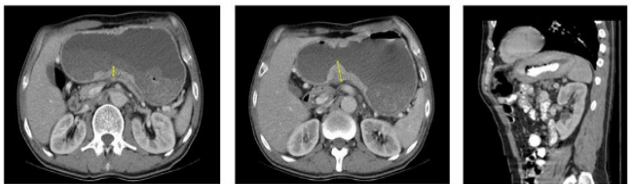

Figure 1: Grades of gastric wall thickening on computed tomography images. A- Moderate (5-20 mm) thickening B- Severe (20-60 mm) thickening C- Diffuse wall thickening

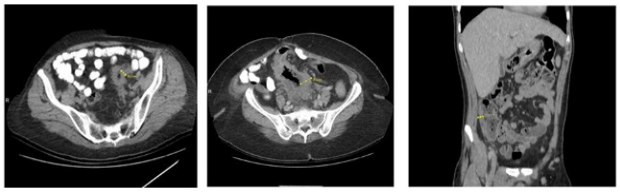

Figure 2: Grades of colonic wall thickening on computed tomography images A- Moderate (5-20 mm) wall thickening of the sigmoid wall B- Severe (20-60 mm) thickening of the sigmoid wall C- Diffuse wall thickening in the caecum and ascending colon

Statistical Analysis

Data analysis was performed using the IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) package program. The Kolmogorov-Smirnov test was used to examine whether the distribution of discrete numerical variables was close to normal. The assumption of homogeneity of variances was investigated using Levene's test. For descriptive analysis, numerical variables were expressed as means±standard deviations, while categorical variables were given as numbers of cases and percentages. The significance of the difference between more than two independent groups was evaluated with Student's t-test and one-way analysis of variance (ANOVA). The categorical data was evaluated by Fisher's exact result probability test, while the Continuity Corrected Chi-Square test was used when the expected frequency was between 5-25. Otherwise, the Pearson test was performed. The p value was considered statistically significant when it was less than 0.05.

RESULTS

A total of 647 patients had undergone an endoscopic or colonoscopic evaluation at our endoscopy unit during the study period. All of these patients had undergone a preceding abdominal CT within one month of the evaluation. The male gender was predominant, with 414 (63,9%) male patients in the study cohort. The patients' demographic characteristics, including chief complaints and duration of symptoms, are displayed in Table 1. One hundred and six (16.38%) patients had undergone an endoscopy, while 541 (83.62%) had undergone a colonoscopy. Among the patients who underwent an endoscopy, the most common chief complaint was dyspepsia (n=60, 56,6%) and for those who underwent a colonoscopy, the most frequent chief complaint was an unexplained change in bowel habits (n=389,71,9%). The mean duration of symptoms was 33±5 days.

Table 1. Demographic characteristics of the study patients

Mean age (years)	61.6±13.9	
Gender	N=647	(%)
Male	414	63.38
Female	233	83.72
Chief complaints before endoscopy	N=106	(%)
Dyspepsia	60	56.60
Weight Loss	53	50.00
Dysphagia	23	21.69
	N=541	(%)
Unexplained change in bowel habits	389	71.90
Bloating- abdominal cramps	258	47.69
Lower gastrointestinal bleeding	112	20.70
Mean duration of symptoms	33 ± 5 days	

The median age was 60.3±13.1 years in the endoscopy group and there were 66 (62,3%) males and 40 (37,7%) females in this patient

group. The evaluations revealed that most endoscopic lesions were located in the stomach's antrum (n=56, 52,8%). This was followed by corpus (n=45, 42,5%), cardia (n=26, 24,5%) and fundus (n=9, 8,5%). Seven (6,6%) patients were reported to have lesions at the lower esophagus. The endoscopic biopsies were malignant in 101 patients (95,3%) and benign in 5 (4,7%) patients. The most common pathology was adenocarcinoma (n=71, 66,9%). Signet ring cell carcinoma, malignant epithelial tumors and neuroendocrine tumors were detected in 16 (15,1%), 8 (7,5%), and 3 (2,8%) of these patients, respectively (Table 2).

Table 2. Biopsy results of the patients in the endoscopy group

Endoscopic biopsy results	(n=106)	(%)
Adenocarcinoma	71	66.9
Signet ring cell carcinoma	16	15.1
Malignant epithelial tumor	8	7.5
Neuroendocrine tumor	3	2.8
Squamous cell tumor	1	0.9
Gastrointestinal stromal tumor	1	0.9
Mixed (Adenocarcinoma and Signet cell carcinoma)	1	0.9
Benign	5	4.7

A review of these 106 patients' CT sections showed thickened wall in 93 (87.7%) patients. The CT sections of the remaining 13 (12.3%) patients were normal. Comparison of the patients with and without a thickened wall on CT scan revealed no difference concerning age, gender distribution and malignancy rates (p=0.976, p=0.231, p=0.487, respectively) and are presented in Table 3. The analysis regarding lesion locations elucidated that CT findings and endoscopic findings overlapped in 70 patients (66,03%). However, in 23 (21,7%) patients, the location information showed no conjunction between endoscopy and CT. Classification of the patients concerning the grade of wall thickening revealed that wall thickness was normal in 13 (12,3%), moderately increased in 16 (15,1%) and severely increased in 13 (12,2%) patients. Sixty-four (60,4%) patients had diffusely increased wall thickness. There was no difference between these patient subgroups concerning patient age and malignancy rates (p=0.656, p=0.344). On the other hand, there was a statistically significant difference between these subgroups regarding gender distribution (p=0.049) (Table 3).

Table 3. Comparison of the endoscopy results and patient demographics based on the presence and grade of wall thickening

Presence of thickened wall	Age (years)	Male/Female (n)	Benign/ Malignant (n)
-No	60.4±11.2	6/7	1/12
-Yes	60.3±13.4	60/33	4/89
p-value	0.976	0.231	0.487
Grade of wall thickening	**Age (years)**	**Male/Female (n)**	**Benign/ Malignant (n)**
-Normal (0-5 mm)	60.4±11.2	6/7	1/12
-Moderate (5-20 mm)	59.6±13.3	10/6	0/16
-Severe (20-60 mm)	56.2±11.7	12/1	0/13
Diffuse wall thickening	61.3±13.8	38/26	4/60
p value	0.656	0.049	0.344

The mean patient age was 62.7±12.7 years in the colonoscopy group (Table 5). Among the 541 patients included in this group, 348 (64,3%) were males and 193 (35,7%) were females. Normal colonoscopic findings were detected in 8 (1,5%) patients. The colonoscopic evaluations revealed that 158 (29,2%) patients had lesions in the rectum, 91 (16,8%) patients in the sigmoid colon and 53 (9,8%) patients in the caecum. On the other hand, 37 (6,8%) patients had lesions in the ascending colon, 35 (6,5%) patients in the descending colon, 35 (6,5%) patients in the hepatic flexure, 27 (5%) patients in the splenic flexure and 20 (3.7%) patients in the transverse colon. Increased colonic wall thickness was detected in 506 (93,5%) of the CT sections. Analysis of the CT findings and colonoscopic lesion locations revealed that they overlapped in 432 (79,8%) patients (p=0.082).

Normal or benign colonoscopic biopsy findings were reported in 19 (3,5%) patients. Adenocarcinoma was detected in 456 (84,2%), adenoma (tubular/ villous) in 36 (6,6%), mucinous adenocarcinoma in 21 (3,8%) and signet cell carcinoma was detected in 8 (1,4%) patients. Squamous cell carcinoma was diagnosed in 1 patient (0,2%) (Table 4). Comparison of the patient groups with or without wall thickening did not reveal any significant differences regarding age, gender distribution and malignancy rates (p=0.578, p=0.469, p=0.13, respectively) (Table 5).

Thirty-four (6,2%) patients had standard colonic wall measures. Colonic wall thickness was moderately increased in 61 (11,2%), severely

increased in 42 (7,7%) and diffusely increased in 394 (72,8%) patients. There was no difference between the patient subgroups with different colonic wall thicknesses regarding patient age, gender distribution and malignancy rates (p=0.833, p=0.147, p=0.528, respectively) (Table 5).

Table 4. Biopsy results of the patients in the colonoscopy group

Colonoscopic biopsy results	(n=541)	(%)
Adenocarcinoma	456	84.2
Adenoma (tubular/villous)	36	6.6
Mucinous adenocarcinoma	21	3,8
Normal findings/benign conditions	19	3.5
Signet cell carcinoma	8	1.4
Squamous cell tumor	1	0.2

Table 5. Comparison of the colonoscopy patients based on presence and grade of wall thickening

Presence of thickened wall	Age (years)	Male/Female (n)	Benign/ Malignant (n)
No	61.5±13.8	24/10	3/31
Yes	62.7±12.6	323/183	17/479
p value	0.578	0.469	0.130
Grade of wall thickening	Age (years)	Male/Female (n)	Benign/ Malignant (n)
Normal (0-5 mm)	62.4±13.0	24/10	3/31
Moderate (5-20 mm)	62.6±11.5	48/15	2/59
Severe (20-60 mm)	64.4±11.9	27/16	1/41
Diffuse wall thickening	62.5±12.9	249/152	14/380
p value	0.833	0.147	0.528

DISCUSSION

To the best of our knowledge, no prospective clinical trials were conducted, and consensus clinical guidelines reported, to resolve the dilemma regarding the management of the patients with gastrointestinal wall thickening on CT. Moreover, the use of CT for non-specific gastrointestinal symptoms such as dyspepsia, weight loss, unexplained change in bowel habits, bloating and abdominal cramps, has increased significantly over the last decade due to its wide availability [13]. Therefore, a thickened gastrointestinal wall has become a common finding in the daily practice of clinicians and these typically consult gastroenterology or general surgery in these cases. As a result, these patients undergo invasive procedures, such as endoscopy or colonoscopy, and bear the potential risks of these investigations [14].

In our study, dyspepsia was the leading complaint in patients undergoing endoscopic procedures, whereas an unexplained change in bowel habits was the leading complaint in those undergoing colonoscopies. The increased volume of patients with complaints of chronic diarrhea or constipation and dyspepsia, raises the question of endoscopic evaluations as part of the diagnostic workup regarding these increasingly prevalent complaints [15]. On the other hand, for patients with digestive complaints, endoscopic evaluations have set the gold standard. Wood et al. analyzed 300 consecutive patients with digestive complaints and concluded that an endoscopy was unlikely to uncover a diagnosis to explain altered bowel habits or dyspepsia [16]. However, they recommended an initial non-invasive workup, such as a CT scan, as a reasonable option to identify a likely diagnosis. Some clinical studies investigated the association between an incidental finding of gastrointestinal wall thickening on CT scan and endoscopic findings (2, 3, 9-12, 14, 16).

However, most of these studies did not analyze the symptomatology of the patients. In our study, we reviewed the gastrointestinal symptoms and chief complaints of our patients. Al-Khowaiter et al. retrospectively evaluated the clinical and endoscopic findings of patients previously reported to have bowel wall thickening on CT [17]. They reported that 24% of these patients had normal colonoscopic findings. In our series, only 4,7% of the endoscopic procedures and 1,5 % of the colonoscopic procedures revealed normal results. On the other hand, 95,3% of the endoscopies and 96,5 % of the colonoscopies elucidated a premalignant or malignant lesion. This relatively high premalignant and malignant lesion detection rate in our study can be attributed to the fact that our institution is a tertiary referral center for patients with gastrointestinal diseases. Additionally, in our study, the mean patient

was higher than the mean age of the study patients of the study population of Al-Khowaiter et al. [17]. Since the gastrointestinal malignancy rates increase with increasing patient age and gastrointestinal malignancies are most frequently diagnosed in the sixth and seventh decades, this

fact should have contributed to our relatively higher gastrointestinal malignancy detection rate.

Our analysis revealed that CT and colonoscopic findings overlapped in 79,8% of the patients. Stermer et al. reported that among twelve cases with a diverticular disease diagnosed by colonoscopy, only eight had colonic wall thickening on CT [18]. Cai et al. reviewed the patients with incidental radiological findings of gastrointestinal wall thickening who subsequently underwent endoscopic procedures [19]. Their study demonstrated significant colonoscopic abnormalities in the sigmoid colon and rectum in 96% of patients with the radiological finding of wall thickening in the exact location. Similarly, endoscopic findings overlapped with CT in 66,3% of the patients in this study.

Among our patients, 95,3% were found to have a malignant pathology. In the literature, the accuracy for diagnosing gastric cancer in preoperative CT scans was reported to be in the range of 69-85%. However, this accuracy level decreased to 26-53% in patients with the early stages of gastric malignancies. Also, Akbas et al. noted that the antropyloric region was challenging to evaluate regarding increased wall thickness associated with gastric malignancies due to its anatomical and physiological characteristics [3]. The peristaltic movements in this region and the physiological thickness of the antral smooth muscle can be confounding.

In our study, the appearance of a thickened gastrointestinal wall on the CT scan was not associated with an increased malignancy rate. This finding might be due to the high malignancy rate in our series. Moreover, the grade of wall thickening was also not associated with malignant disease. In their retrospective study, Tongdee et al. measured the wall thickness in patients with and without gastrointestinal malignancy as 16.64 and 5.68, respectively [20]. The difference was found to be statistically significant between the groups. The same study utilized a ROC curve analysis to determine the optimal cut-off value and suggested a 10mm cut-off point for differentiating malignancy. Our study took a cut-off point of 5mm, as reported in the literature [21].

Our study has some limitations which need to be considered while evaluating its findings. First, it is a retrospective study. Second, it bears a risk of selection bias since all patients presenting with gastrointestinal complaints do not automatically undergo abdominal CT scans. As a result of this approach, it can be stated that patients who underwent an abdominal CT scan and were included in our study may have had more severe findings and more severe disease. Third, the indications of ordering an abdominal CT scan in patients with gastrointestinal symptoms are not identified. Also, it is known that CT measurement of gastrointestinal wall thickness can be affected by some parameters such as distention and slice increments of the CT scan. These variables may have led to inter-observer differences in these measurements. Fourth, the time interval between abdominal CT scan and endoscopic or colonoscopic investigations was not standard. Therefore, the disease processes leading to wall thickening detected on CT scans might have partially or entirely healed in cases with long intervals.

Despite these limitations, we suggest performance of endoscopic or colonoscopic evaluations in patients with gastrointestinal wall thickening in CT scans since the diagnostic and predictive accuracy are limited when a single test like CT is used.

CONCLUSIONS

Endoscopic-colonoscopic evaluations should be performed in patients with gastrointestinal wall thickening in CT scans, since the diagnostic and predictive accuracy are limited when a single test like CT is used.

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RESEARCH ARTICLE

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The Effects of NLR on the Diagnosis and Pharmacological Management of Brain Abscesses

NLO'nun Beyin Apselerinin Tanı ve Farmakolojik Tedavi Yönetimine Etkileri

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ABSTRACT

Aim: The present study aims to examine the effectiveness of the neutrophil-to-lymphocyte ratio in the treatment and diagnosis of patients with brain abscesses.

Methods: In this retrospective study, radiological, neurological, and surgical data obtained from the medical records of healthy volunteers (n = 10) who presented to the hospital for check-ups and patients with brain abscesses who were treated (n = 10) were evaluated statistically. Alpha significance value was accepted as <0.05.

Results: Comparisons between groups revealed that the erythrocyte sedimentation rate, C-reactive protein, leukocyte, and neutrophil values were statistically significant (P <0.05) while lymphocyte value was not statistically significant (P >0.05). The preoperative neutrophil-to-lymphocyte ratio in cases diagnosed with brain abscesses showed statistical significance compared to that in the healthy volunteers (P <0.05) and the neutrophil-to-lymphocyte ratio increased 3.31-fold in the study group compared to the healthy volunteers.

Conclusion: A strong positive strong relationship between the neutrophil-to-lymphocyte ratio and abscess size (r = 0.662; P = 0.037) was observed. An increased neutrophil-to-lymphocyte ratio may serve as an early warning signal of brain abscesses.

Keywords: Antibiotic treatment; brain abscess; low-cost diagnosis method; magnetic resonance image; neutrophil-to-lymphocyte ratio

ÖZ

Amaç: Bu makalede; beyin apsesi tanısı alan olgularda, nötrofil-lenfosit oranı (NLO)'nın, tanı ve tedavide önemli olup olmadığının incelenmesi amaçlandı.

Metot: Retrospektif dizayna sahip araştırmada, hastaneye kontrol için gelen sağlıklı bireyler (n=10) ile beyin apsesi olan ve tedavi edilen olgular (n=10)'dan elde edilen radyolojik, nörolojik ve cerrahi veriler istatistiksel olarak değerlendirmeye alındı. Alfa anlamlılık değeri <0,05 olarak kabul edildi.

Bulgular: Gruplar arası karşılaştırmalar sonucunda; eritrosit çökelme oranı (ESR), C-reaktif protein (CRP), lökosit (WBC) ve nötrofil (NEU) değerleri istatistiksel olarak anlamlı iken (P<0,05), lenfosit (LYMPH) değerinde istatistiksel olarak anlamlılık görülmedi (P>0,05). Sağlıklı bireylere oranla beyin apsesi tanısı alan olgulara ait preoperatif NLO değerlerinin istatistiksel olarak anlamlılık (P<0,05) gösterdiği ve NLO değerinin sağlıklı bireylere oranla yaklaşık 3,31 kat artış gösterdiği kaydedildi.

Sonuç: NLO oranı ile abse boyutu arasında (r=0,662; P=0,037) pozitif yönde kuvvetli ilişki bulunmaktadır. Artış gösteren NLO, beyin apsesinin tanısında erken uyarı sinyali olarak hizmet edebilir.

Anahtar Kelimeler: Antibiyotik tedavisi, beyin apsesi, manyetik rezonans görüntüleme, düşük maliyetli tanı metodu, nötrofil-lenfosit oranı.

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INTRODUCTION

Brain abscesses are focal infections of the central nervous system that begin in a localized area of the brain parenchyma and gradually develop into an intra-axial collection of encapsulated pus [1]. Brain abscesses can occur through direct extension, where the infection spreads from a nearby area, or via hematogenous dissemination, where the causative pathogen spreads from distant organs to the cerebral tissue. A brain abscess develops from a suppurative focus of infection (mastoiditis, chronic otitis media, frontoethmoidal sinusitis, or dental infections), or a distant site of infection (lungs, skin, endocarditis, intra-abdominal abscess, urinary tract infection) [2]. It can also occur directly following head trauma or cranial surgical procedures. However, the focus of infection is not identified in 20–30% of cases [2].

Diagnosis of a brain abscess is very challenging if the patient does not have clinically evident neurological findings [3]. The most common symptoms are fever, headache, and vomiting [2]. Brain abscesses may initially present clinical symptoms, such as headaches, new epileptic seizures, and focal neurological deficits [2]. The most common symptoms are headache (69%), fever (45%), and nausea and vomiting (40%), respectively [2, 4]. Diagnosis and therapeutic management can sometimes be difficult even in patients with neurological findings [1]. Radiological imaging methods play a primary role in the differential diagnosis of brain abscesses from other intracranial pathologies [1]. The conventional magnetic resonance imaging (MRI) method is an indispensable tool for the identification of lesions and their localization and morphological features, but conventional MRI cannot credibly distinguish brain abscesses from other intracranial mass lesions, such as necrotic tumors [1].

The most common causative pathogens in brain abscesses are associated with paranasal sinusitis, which is generally caused by the Streptococcus milleri group (both aerobic and anaerobic) organisms [5]. Haemophilus, Bacteroides species, Staphylococcus aureus, and Enterobacteriaceae are also described as causative pathogens of brain abscesses [5]. The most common pathogens found in intracerebral abscesses may result from those caused by dental infections due to streptococci, Bacteroides fragilis, and Fusobacterium species [5].

Commonly used pharmaceuticals in the treatment of central nervous system infections are adjuvant corticosteroids and antibiotics, including ampicillin, cefepime, cefotaxime, ceftriaxone, gentamicin, meropenem, metronidazole, nafcillin, penicillin G, rifampin, and vancomycin. Vancomycin is also suitable for intraventricular administration, with an adult dose of 20 mg/day, or a pediatric dose of 10 mg/day [2].

The neutrophil-to-lymphocyte ratio (NLR) has been gaining traction recently, and has widely been accepted as an accurate marker of inflammatory status [6, 7]. The effectiveness of NLR, routinely used as a marker of infection like other markers, such as leukocyte (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), has yet to be investigated for brain abscesses in the literature. The role of the NLR has largely remained unexamined. The present study aims to address the NLR in the treatment and diagnosis of patients with brain abscesses.

MATERIALS AND METHODS

Selection Criteria

Neurological and radiological examinations were performed with patients admitted to the clinic with headaches, nausea/vomiting, or epileptic seizures between January 01, 2014, and December 31, 2020. A total of 218 patients with intracranial lesions were operated on. Of the patients who underwent surgery, 14 were diagnosed with brain abscesses and received inpatient treatment. Patients with rheumatoid arthritis (n = 1), patients with membranous glomerulonephritis who received immunosuppressive therapy (n = 1), and patients with brain abscesses who were referred from an external healthcare unit and received oral antibiotic treatment (n = 2) were excluded from the study. Data from the remaining cases (n = 10) were used.

Study Design and Accumulation of Data

Demographic data and clinical features were recorded and listed using Microsoft Excel. Patients

with any other condition that could potentially contaminate ESR, CRP, or white blood cell (WBC) data and those with incomplete lab results were excluded. The control group included patients admitted to the hospitals for a routine physical check-up, who did not have any serious disease or malignancy, and no history of glucocorticoid use. The control group was compatible with the brain abscess groups in gender distribution (n = 10). The preoperative and postoperative data of the cases included in the study were compared with the data of the control group.

Neurological Examination

The most common symptoms of the patients with brain abscesses were headache, fever, focal neurological deficit, nausea/vomiting, epileptic seizures, and changes in consciousness.

Radiological Examinations

Radiological examinations were performed using a General Electric (GE) HDxt 1.5 Tesla (1.5T) MRI scanner. The patients were instructed to lie down in the supine position, and a head coil was used before the MRI. The images of T1-weighted, T2-weighted, FLAIR in the axial plane, T1-weighted in the coronal plane, T2-weighted in the sagittal plane, and T1-weighted sequences in the axial and coronal planes after intravenous injection (IV) of gadolinium were then acquired. Diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) sequences were also obtained.

Surgical Technique

All patients were operated on by the same surgeon, and different surgical methods were used. In the first surgical method, a burr-hole was made in the calvarium, and then the dura mater was incised so that the pus could be aspirated out. In the second surgical method, patients underwent craniotomy, the abscess was reached through a dural incision or trans-cortical or trans-sulcal resection, and the aspiration of liquid pus was performed. In the third surgical method, the capsule of the abscess was also excised, along with the procedure described for the second surgical method. In cases with intracranial multiple abscesses, successful abscess drainage was achieved by performing two different craniotomies in the same session. One patient underwent craniotomy and abscess drainage. However, upon the recurrence of the abscess, this patient was operated on twice. The follow-up of the same patient revealed the development of hydrocephalus, and an external ventricular drainage catheter was placed.

Statistical Analysis

Data management and statistical analysis were performed using Minitab Software (Version 22.0). Demographic data are presented as mean ± standard deviation (SD). Tukey's honestly significant difference test was used after the one-way analysis of variance (ANOVA) for comparisons between groups. The direction and strength of the linear association between the data were evaluated using the Pearson correlation coefficient. The alpha significance value was accepted as $P < 0.05$.

RESULTS

Of the initial cohort of 218 patients, 14 (6.4%) were diagnosed with brain abscess. The average age of the control group patients (n = 10), of whom 30% were female, was 40.0 ± 18.87 years. The average age of the study group patients (n = 10), of whom 30% were female, was 39.1 ± 22.33 years. The average body temperature of the study group patients was 37.58 ^{o}C.

Neurological Findings

Four patients had epileptic seizures, two patients had headaches, three patients had vomiting, one patient had a fever, and one patient had cranial nerve involvement. Six patients were conscious, two patients were unconscious, and two patients had somnolence. Two patients who were unconscious and sleeping prone died, and the state of consciousness and neurological dysfunction at the time of the first presentation affected mortality in patients with brain abscesses (Table 1).

Radiological Findings

Table 2 shows the locations and sizes of the abscesses in the patients. Figure 1 presents the MRI sections of a 38-year-old male patient with a multifocal abscess in the brain (Table 2, Figure 1).

Table 1. Data on Neurological Assessment.

Presenting Complaint	Loss of Consciousness	Meningeal Irritation Sign	Cranial Nerve Involvement	Motor Deficits	Predisposing Factors
Seizure	None	None	None	None	Chronic renal failure
Vomiting, fever	Somnolence	Stiff Neck	None	None	Otitis media*
Vomiting, ear pain	None	None	None	None	Beta thalassemia + Otitis media*
Headache	None	None	None	None	Sinusitis
Seizure, headache	None	None	None	None	None
Seizure	None	None	None	None	Membranous granulonephritis + T2DM
Ataxia, vomiting	Yes	None	None	None	Otitis media *
Seizure	None	None	None	Left hemiparesis	Operated frontal tumour
Diplopia, dysphagia	Somnolence	None	Ptosis, diplopia	None	Myasthenia gravis + T2DM
Loss of Consciousness	Yes	None	None	No motor response	Trauma

*: Patients died.

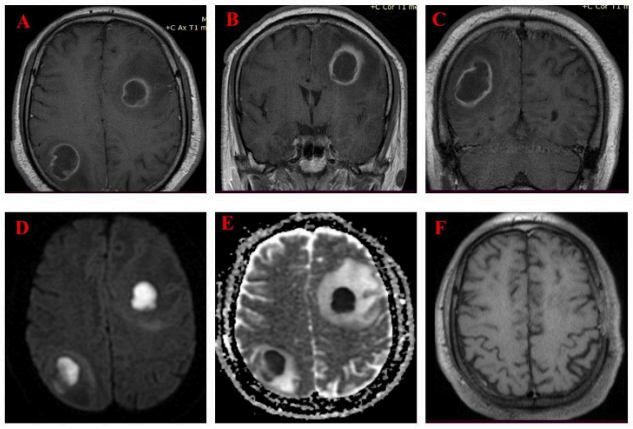

Figure 1. MRI Findings.

Figure 1A: A 38-year-old male patient's axial T1-weighted MRI sections at the supraventricular show the lesions in the left frontal lobe at the level of white matter and at the posterior of the right parietal lobe in the junction of white matter and gray matter. The lesions compatible with abscesses are smooth-lobule-contoured, accompanied by millimetric mural enhancement on the posterior wall, a rather smooth inner wall, and a peripheral ring-shaped enhancement pattern. The central portion of the lesions is relatively homogeneous and hypointense, and a diffuse signal loss due to vasogenic edema and effacement of adjacent sulci in the periphery of the lesion are observed. A minimal shift is also seen in the midline structures due to the left frontal lesion.

Figure 1B: The coronal plane images of the abscess in the left frontal lobe described in Figure 1A show that the inner wall of the abscess is smooth, and the outer wall is partially thick and partially uniformly contrasting. A diffuse signal loss in the white matter due to vasogenic edema and effacement of adjacent sulci in the periphery of the lesion are observed. A minimal compression in the lateral ventricle of the left frontal horn and a slight right shift in the midline structures are also seen.

Table 2. Locations of abscesses and size of the abscesses drained out.

Abscess Location	Abscess Size (mm)
Right Parietal	20x10
Left Frontal + Left Caudate Nucleus	19x8.5
Right Temporal	6,5x4.5
Left Frontal	30x19
Left Frontal + Right Occipital	32x28
Left Frontal	28x17
Right Cerebellar	45x35
Right Frontoparietal	38x25
Right Parietal + Left Parietal	43x28
Left Occipital	37x29

Figure 1C: The coronal plane images of the abscess in the right parietal lobe described in 1A show the abscess with irregular lobule-contoured and peripheral ring-shaped enhancement. A diffuse signal loss in the white matter due to vasogenic edema, effacement of adjacent sulci in the periphery of the lesion, and narrowing of the lateral ventricle of the right occipital horn are also observed.

Figures 1D and E: An increased signal in the left frontal lobe and central right parietal lesion is observed in the left DWI sequence. A decreased signal on the ADC map indicates diffusion restriction, which is a significant sign in the diagnosis of an abscess. Extensive edema is also seen around the lesion.

Figure 1F: Axial T1-weighted MR images obtained

following gadolinium IV in the sixth postoperative month of the same patient reveal disappearance of the abscesses in the left frontal and right parietal portion. No edema is observed in the brain parenchyma. The normal configuration of sulci and a postoperative craniectomy defect are also seen in the left frontal bone.

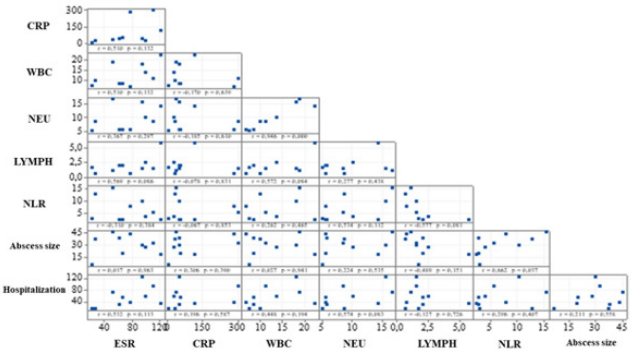

Figure 2. Statistical evaluation of all biochemical parameters and Pearson correlation in the patients with brain abscess

Evaluation of Biochemical Data

The mean values of ESR, CRP, WBC, NEU, LYMPH, and NLR in the control group were 7.6 ± 5.21, 1.39 ± 1.13, 7.01 ± 2.45, 4.23 ± 1.79, 2.13 ± 0.54, and 2.02 ± 0.66, respectively. The mean preoperative values of ESR, CRP, WBC, NEU, LYMPH, and NLR in the study group patients were 72.8 ± 33.94, 96.00 ± 106.54, 12.45 ± 5.49, 9.55 ± 4.38, 1.95 ± 1.45, and 6.69 ± 4.66, respectively (Table 3).

A strong positive correlation was observed between NEU and WBC (r = 0.946; P = 0.05) and between NLR and abscess size (r = 0.662; P = 0.037).

Biochemical parameters were higher in patients with preoperative brain abscesses (Figure 3).

The comparisons between groups revealed that ESR (F = 17.99; P = 0.00), CRP (F = 3.43; P = 0.047), WBC (F = 3.60; 0.041), and NEU (F = 5.20; P = 0.012) were statistically significant (P <0.05), while LYMPH (F = 0.40; P = 0.677) was not statistically significant (P >0.05).

The preoperative NLR values (Adj SS = 115.5; Adj MS = 55.76; F = 5.28; P = 0.012) of the patients with brain abscesses were statistically significant as compared to those of the healthy volunteers (P <0.05) (Table 4).

The histopathological evaluations of a 38-year-old male patient who underwent craniotomy and abscess drainage were presented demonstratively (Figure 4).

The culture results of the study group revealed no bacterial growth in two cases and the growth of anaerobic gram-positive cocci in two cases. Gram-negative anaerobe and beta-hemolytic Streptococcus growth were observed in one case. The growth of gram-positive diplococcus (n = 1), Streptococcus spp (n = 1), Nocardia (n = 1), Pseudomonas aeruginosa (n = 1), and Coryneform-like bacteria (n = 1) were seen in the remaining cases.

Table 3. Comparison of biochemical parameters between groups.

Groups	Age (years)	Sex	ESR (mm/ hour)	CRP (mg /L)	WBC (µl/ ml)	NEU (µl/ ml)	LYMPH (µl/ml)	NLR
Volunteers (n=10)	28	M	6	1.39	6.9	4.06	2.34	1.73
	38	F	10	3.86	6.56	4.3	1.69	2.54
	36	M	4	1.81	6.82	4.03	2.23	1.80
	33	M	5	0.53	6.84	3.78	2.46	1.53
	31	M	9	0.59	6.08	2.75	2.7	1.01
	40	M	21	0.84	13.59	8.85	3.13	2.82
	47	M	8	1.68	6.59	3.98	1.86	2.13
	59	M	5	2.52	5.26	3.43	1.35	2.54
	47	F	5	0.24	6.96	4.88	1.7	2.87
	41	F	3	0.45	4.48	2.23	1.84	1.21
Preoperative cases (n=10)	51	M	66	55.8	8.31	5.59	2.03	2.75
	3	F	121	118	22.24	14.2	5.72	2.48
	16	F	22	6.6	7.47	5.15	1.73	2.97
	22	M	94	50.1	18.01	15.5	1.51	10.26
	38	M	111	299.05	11	8.51	1.5	5.67
	56	M	99	30.4	13.7	10.02	2.48	4.04
	62	M	51	36.81	18.92	16.5	1.08	15.27
	43	F	61	50.5	8.3	5.75	2.06	2.79
	74	M	77	282	6.7	5.61	0.71	7.90
	26	M	26	30.76	9.8	8.68	0.68	12.76
Postoperative Cases (n=10)	51	M	32	14.9	8.31	4.55	2.21	2.05
	3	F	31	290	1.11	0.22	0.84	0.26
	16	F	42	173	20.47	15.3	3.83	3.99
	22	M	29	1.1	5.5	2.41	1.91	1.26
	38	M	55	12.39	5.04	2.6	1.75	1.48
	56	M	89	1	12.57	8.76	2.15	4.07
	62	M	48	103.41	9.37	7.48	1.09	6.86
	43	F	33	7.7	5.9	3.33	1.73	1.92
	74	M	1	89.8	4.8	3.53	0.69	5.11
	26	M	9	0.6	11.8	10.1	0.97	10.41

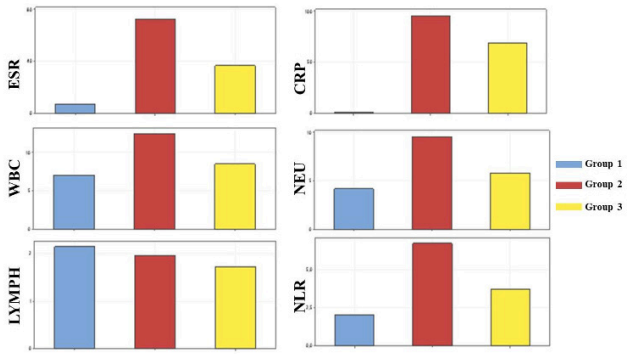

Figure 3. Group 1; healthy volunteers, group 2; preoperative evaluation of patients, and group 3: postoperative evaluation of patients

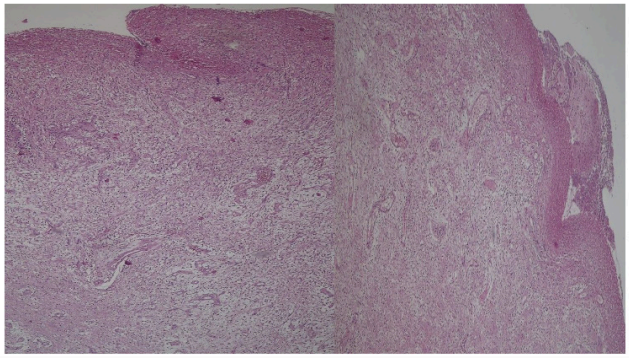

Figure 4. Haematoxylin&Eosin (H&E) staining is examined under a light microscope at a magnification of 40X and an image of gliosis.

Table 4. Comparison of intergroup NLR values with Tukey's HSD test after one-way ANOVA. Grouping information using the Tukey Method and 95% confidence interval.

Groups	N	Mean	Grouping
Group 1 (Volunteers)	10	2.02322	B
Group 2 (Preoperative cases)	10	6.69268	A
Group 3 (Postoperative cases)	10	3.74530	A B

Antibiotherapy and combined corticosteroid therapy were administered to all patients during their hospital stay. The surgical procedure performed and duration of hospital stay are presented in Table 5.

Acyclovir 80 mg / kg / day, ceftriaxone 50 mg / kg / dose IV q12h and vancomycin 17.5 mg / kg / dose IV q6h were administered to the three-year-old patient. The remaining cases were given the following adult doses of antibiotherapy: imipenem (3 g / day), linezolid (30 mg / kg / daily), metronidazole (2000 mg / day), meropenem (6 g / day), ceftriaxone (4 g / d), teicoplanin (400 mg once daily intravenously), cotrimoxazole (15 mg / kg iv of the trimethoprim component per day in three or four divided doses), and vancomycin (60 mg / kg / day). Dexamethasone was given 16 mg / day for 7–14 days with 3–4 dose intervals in adults. In pediatric use, it started with an initial dose of 0.02–0.3 mg / kg with a dose interval of 3–4 and was administered as a maintenance dose of 0.01–0.1 mg / kg.

Table 5. The surgical procedure performed, and duration of hospital stay.

	Applied treatment			Length of Hospital Stay (days)
Cases	Craniotomy	Burr-hole drainage	Antibiotherapy	
Case 1	+	-	Metronidazole + Ceftriaxone + Vancomycin	56
Case 2	+	+	Acyclovir + Ceftriaxone + Vancomycin	37
Case 3	-	+	Metronidazole + Meropenem + Vancomycin	17
Case 4	+	-	Metronidazole + Meropenem + Vancomycin	125
Case 5	+	-	Metronidazole + Ceftriaxone + Vancomycin	94
Case 6	+	-	Metronidazole + Ceftriaxone + Imipenem + Trimethoprim / sulfamethoxazole	59
Case 7	+	-	Metronidazole + Meropenem + Teicoplanin	75
Case 8	+	-	Ceftriaxone	32
Case 9	+	-	Metronidazole + Ceftriaxone + Vancomycin	38
Case 10	+	-	Meropenem + Linezolid	18

DISCUSSION

Brain abscesses affect all age groups and are not specific to a particular country, race, or geographic place [8]. It is a disease that had a high morbidity and mortality rate in the past [8], but advances in medical technology and expertise in this field have significantly improved outcomes. The causal organisms are diverse and have evolved [8]. The

treatment of brain abscesses is primarily based on antimicrobial therapy, but surgical intervention and abscess drainage play pivotal roles in achieving positive results [8].

Brouwer et al. [9] argued that many studies in this field were restricted by methodology and that the outcomes were less beneficial for clinical practice. The authors suggested that advancements in brain imaging methods, surgical procedures, and antibiotic treatment had significantly improved the outcomes of patients with brain abscesses [9]. However, it is important to make a correct and rapid diagnosis to start treatment as soon as possible.

Today, radiological imaging techniques are frequently used in the differential diagnosis of cerebral abscesses. In particular, contrast-enhanced cranial MRI is a highly useful radiological examination in the diagnosis of cerebral abscesses [10]. The peripheral ring-like enhancement pattern is considered a characteristic finding in the diagnosis of cerebral abscesses, but this is insufficient in the differential diagnosis of primary malignant cerebral tumors with dense necrotic areas. Therefore, DWI and MR spectroscopy are used extensively in the differential diagnosis of cerebral abscesses. Despite the advances and developments in all these imaging methods, both early differential diagnosis and urgent treatment of the disease, which have a direct effect on the prognosis, remain a major problem. Moreover, the difficulties in the diagnosis of cerebral abscesses may delay microbiological evaluations of the causative pathogens involved in the development of the abscess. Therefore, the question of NLR's importance in the diagnosis and treatment of patients with brain abscesses must be examined.

Afari et al. [11] stated that NLR is now considered a low-cost biomarker with effective clinical predictability and a positive effect on prognosis, even though it was described decades ago. Some studies have reported an incidence of brain abscesses between 0.4 and 2.7 per 100,000 [9, 12–14]. A total of 14 out of 218 cases were diagnosed with brain abscesses (6.4%) in the present study.

MRI is a more sensitive radiological examination than CT in the detection of brain abscess. MRI is a very sensitive method that allows visualization of the changes in the tissue water content, creates a distinct contrast between the edematous brain and normal brain tissue, and helps in the diagnosis of cerebritis and abscess [15]. Characteristic features of the brain abscess observed in MRI are that the central part of the abscess is hyperintense on the T2-weighted sequence and hypointense on the T1-weighted sequence compared to the cerebrospinal fluid. Vasogenic edema encircling the lesion is described by surrounding hypointensity on the T1-weighted sequence and hyperintensity on the T2-weighted sequence [15, 16]. It also has a smooth capsule surrounding the abscess. This capsule is observed as iso-hypointense on the T2-weighted sequence and has an enhanced contrast in postcontrast images. The classic ring-like enhancement of the abscess capsule is a characteristic finding in CT and conventional MRI, but it is not an abscess-specific finding. It can also be seen in brain tumors, metastases, infarcts, hematoma, and, more rarely, thrombosed giant aneurysms, radiation necrosis, and demyelinating diseases. Common radiological features of abscesses include a 2–7 mm thick, continuous, smooth wall, T2 hypointense capsule, and a smooth thin medial wall. However, these features may not be present in all abscesses, and none of them are 100% specific [15, 16].

DWI helps distinguish neoplasm from a pyogenic abscess. The restricted diffusion within the central non-enhancing portion of the abscess is pathognomonic, but not specific. This is rarely seen in brain cystic or necrotic tumors.

Some researchers have suggested that restricted diffusion in brain abscesses occurs due to necrotic debris, macromolecules, and pus viscosity [15, 17]. Some studies have reported that an increased ADC value may be seen in treated abscesses, and persistent or recurrent ADC may be an indicator of inadequate treatment or reactivation of infection [15, 18].

In the present study, the diagnosis of brain abscesses was made using some pathognomonic but non-specific findings described for abscesses during radiological examinations. The walls of the abscess were thin, and the inner walls were smooth. The images obtained following the

contrast agent injection revealed a peripheral enhancement pattern of the smooth, thin capsule in all lesions. Reduced loss of signal intensity was observed on the T1-weighted sequence, which was compatible with vasogenic edema around the lesions. An increase in the signal intensity on the DWI sequence, which was compatible with restricted diffusion, and a loss of signal intensity on the ADC sequence were also observed.

In recent studies, genetic variation has been associated with the risk of brain abscess [9]. A study in this field reported that single nucleotide polymorphisms in the ICAM-1 and MCP-1 genes escalated susceptibility [9]. However, no genetic testing was performed to evaluate the genetic variation. Many studies have investigated bacterial brain abscesses, and the reported studies on nonbacterial brain abscesses are limited. One meta-analysis revealed that the causative organism could be identified in 68% of brain abscess cases, and in 23% of positive cultures, multiple bacteria were identified. Most culture-positive cases were due to streptococcal (34%) and staphylococcal species (18%) [9].

In this study, the culture results revealed no bacterial growth in two cases and the growth of anaerobic gram-positive cocci in two cases. Gram-negative anaerobe and beta-hemolytic Streptococcus growth were observed in one case. The growth of gram-positive diplococcus (n = 1), Streptococcus spp (n = 1), Nocardia (n = 1), Pseudomonas aeruginosa (n = 1), and Coryneform-like bacteria (n = 1) were seen in the remaining cases.

Empirical therapy is preferred to treat gram-positive and gram-negative bacteria because of the wide variety of potential pathogens causing brain abscesses. Therefore, an extended-spectrum cephalosporin, such as cefotaxime or ceftriaxone, in combination with metronidazole, is administered to all patients [9]. In patients with immunosuppressive disorders, voriconazole, trimethoprim-sulfamethoxazole, or sulfadiazine are used to cover fungi, yeasts, and toxoplasmosis while awaiting further diagnostics [9].

In the present study, acyclovir, imipenem, linezolid, metronidazole, meropenem, ceftriaxone, teicoplanin, trimethoprim/sulfamethoxazole, and vancomycin were administered intravenously. The advised duration of intravenous antimicrobial therapy in bacterial brain abscess patients is 6–8 weeks [19]. In this study, the average duration of intravenous antimicrobial therapy was seven weeks (55.1 days). In addition to the use of antibiotics, adjuvant corticosteroid treatment was applied [20–22]. A form of corticosteroid, mostly dexamethasone, was also used in the treatment.

Some studies have reported that the duration of antibiotic therapy is determined with the help of MRI and DWI results [23]. It has been suggested that, along with the antibiotic regimen, MRI and DWI are helpful tools in the diagnosis of brain abscesses [1, 24, 25]. In the present study, MRI and DWI were used to diagnosis the brain abscess. However, no data were found in the patients' medical records about whether MRI and DWI were used to determine the duration and regimen of antibiotic therapy.

As a result, the biochemical parameters obtained from the cases included in this study showed that the mean NLR was 2.023 in the control group (healthy volunteers), while this rate was 6.69 in cases with brain abscess. The NLR value, which increased approximately 3.31-fold in the study group compared to the healthy individuals, was statistically significant (P = 0.012). A strong positive relationship was observed between the NLR value and abscess size (r = 0.662; P = 0.037).

Limitations: The retrospective design of our study may be considered as limitations. However, it may contribute to the systematic reviews and meta-analyzes [26] and also clinical practise guidelines which will be done together with other same studies about ıssue [27].

Conclusion: NLR may be used as a cost-effective and reliable biomarker in the diagnosis of brain abscess, along with other infection markers such as WBC, CRP, and ESR. However, further prospective studies and randomized clinical trials are needed to substantiate this conclusion.

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The Pitt-Hopkins Syndrome: Report of 5 Patients and Literature Comparison

Pitt-Hopkins Sendromu: 5 Vaka Sunumu ve Literatür Karşılaştırması

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ABSTRACT

Pitt-Hopkins syndrome (PTHS) is characterized by developmental delay, intellectual disability and behavioral changes, distinctive facial gestalt, and breathing abnormalities. PTHS is caused by deletions or pathological variants in the TCF4 gene located at 18q21.2. In this report, we aimed to describe the clinical and genetic findings of patients diagnosed with PTHS and compare our patients with the literature. Patients who were followed up with severe intellectual disability and a variable association of features previously described as characteristic of the PTHS phenotype in the pediatric neurology clinic of Antalya Training and Research Hospital were screened for TCF4 mutations using next-generation sequencing (NGS)-based tests, between 2017 and 2020. A genetic mutation associated with PTHS was detected in five patients. This paper emphasis on mutational and clinical spectrum of PTHS and its significant part in the differential diagnosis of severe mental retardation

Keywords: Angelman syndrome; breath-holding episode; intellectual disability; Pitt-Hopkins syndrome; TCF4

ÖZ

Pitt-Hopkins sendromu (PTHS) gelişimsel gecikme, mental retardasyon ve davranış değişiklikleri, belirgin yüz görünümü ve solunum anormallikleri ile karakterizedir. PTHS, 18q21.2'de bulunan TCF4 genindeki delesyonlardan veya varyantlardan kaynaklanır. Bu yazıda PTHS tanısı alan hastaların klinik ve genetik bulgularını tanımlamayı ve bulgularımızı literatür ile karşılaştırmayı amaçladık. Antalya Eğitim ve Araştırma Hastanesi pediatrik nöroloji kliniğinde 2017 ve 2020 arasında takip edilen, ağır mental retardasyon ve daha önce PTHS fenotipinin karakteristiği olarak tanımlanan özellikleri taşıyan hastalar, yeni nesil dizileme (NGS) tabanlı testler ile TCF4 mutasyonları açısından tarandı. 5 hastada PTHS ile ilişkili bir genetik mutasyon tespit edildi. Bu yazıda, PTHS'nin mutasyonel ve klinik spektrumuna ve ciddi zihinsel geriliğin ayırıcı tanısındaki önemli kısmına vurgulandı.

Anahtar kelimeler: Angelman sendromu, nefes tutma nöbetleri, Pitt-hopkins sendromu, TCF4, zeka geriliği

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INTRODUCTION

Pitt-Hopkins syndrome (PTHS; MIM #610954) is a rare autosomal dominant disease caused by the haploinsufficiency of the transcription factor 4 (TCF4) gene on chromosome 18q21 [1]. Until now, approximately 500 PTHS patients were reported worldwide[2]. PTHS is characterized by severe developmental delay (DD) with moderate-to-severe intellectual disability (ID) and behavioral disturbances, loss of speech, characteristic facial features, tendency to epilepsy, constipation, high myopia, and episodic hyperventilation and/or breath-holding while awake. PTHS is phenotypically similar to several neurodevelopmental disorders such as Angelman Syndrome (AS) (MIM #105830), Rett Syndrome (MIM #312750), Mowat-Wilson Syndrome (MWS) (MIM #235730), and Alpha-thalassemia/mental retardation, X-linked (ATR-X) Syndrome (MIM #301040) [3].

PTHS diagnosis is based on molecular confirmation of characteristic clinical features. The diagnosis is suspected on clinical findings and confirmed by identification on molecular genetic testing of a heterozygous pathogenic variant in TCF4 or a deletion of the chromosome region in which TCF4 is located (18q21.2) [1]. New variants were classified by using the American College of Medical Genetics and Genomics (ACMG) guideline [4]. In this study, we inspected patients who presented to our clinic with ID and PTHS phenotype, detected five patients with TCF4 mutation and presented genotype-phenotype correlations of the molecularly confirmed cases with PTHS.

MATERIAL AND METHOD

Patients who were followed up with severe ID and a variable association of features previously described as characteristic of the PTHS phenotype in the pediatric neurology clinic of Antalya Training and Research Hospital were screened for TCF4 mutations between 2017 and 2020. The genetic diagnosis was made by investigating the TCF4 gene using next-generation sequencing (NGS)-based tests. To confirm our results, we checked the reading frames by using an integrative genomics viewer (IGV) [5]. All obtained variants were classified by using the American College of Medical Genetics and Genomics (ACMG) guideline [4]. Electroencephalography (EEG), electroneuromyography (EnMG), echocardiography (ECHO), and magnetic resonance imaging (MRI) were performed for all patients with TCF4 mutations. Written informed consent was obtained from all parents of the children, which was approved by our Hospital Ethics Committee (Date: 04.03.2021 number: 1/43).

RESULTS

A total of 67 patients with ID were clinically evaluated and 13 patients were found to have clinical features compatible with PTHS. A genetic mutation associated with PTHS was detected in five patients. These patients were reported as case reports below.

Case 1

The first patient was a 2,5-year-old boy, who was born 3800 gr, by cesarean section, from healthy, nonconsanguineous parents. His prenatal period was uneventful. His head circumference was within normal intervals. During the first year of his life, severe psychomotor delay was observed. He was able to raise his head at 12 months. He was able to walk at age 2 years, but the walking was unsteady and ataxic. The speech was absent. He first presented to medical attention at the age 4 months, with hypotonia and lack of following with eyes. He had breath-holding spells at age 3 months and lasted until age of 7 months. He had a long-standing history of constipation after beginning to complementary foods.

In physical examination, he had a short neck, and facial dysmorphism includes coarse face, bitemporal narrowing, squared forehead, full cheeks, peculiar nose conformation, with a broad nasal bridge, down-turned nasal tip, and flaring nostrils, and M shaped upper lip. He had small hands and feet, pes planus, clinodactyly. He had a smiling appearance and lovable behavior. Stereotypic movements of the hands and the head were observed. Poor eye contact was noted. In the ocular examination, strabismus was detected, retinal and fundus examinations were normal. No abnormalities were detected in routine biochemical examinations, and metabolic studies such as ammonia, ceruloplasmin, homocysteine, folic

acid, vitamin B12, thyroid function tests, plasma amino acid analysis. Abdominal ultrasounds, echocardiography, cranial MRI, EEG, and EMG were normal as well. Conventional cytogenetic analysis and fluorescent in situ hybridization (FISH) analysis for AS were normal. By clinical exome sequencing (CES) analysis, we detected a novel heterozygous c.611-180dupT variant in the TCF4 gene which was classified as pathogenic according to ACMG variant interpretation guideline. The patient was diagnosed with Pitt Hopkins syndrome (OMIM: 610954) with this variant.

Case 2

The patient was a 3-year-old girl, who was born 2650 gr, by cesarean section, from healthy, nonconsanguineous parents. Her prenatal period was uneventful. She had microcephaly, hypotonia, and feeding difficulties and stayed in NICU for one week. She was able to control her head at age 1 year and sit without support at age 2.5 years. She cannot walk or talk.

At the age of 6 months, she was referred to pediatric neurology because of hypotonia and microcephaly. She had breath-holding spells at age of 4 months and lasted until age of 10 months. She suffered from constipation after age of 1 year.

In physical examination, she had a short neck and typical facial dysmorphism; includes coarse face, deep-set eyes, strabismus, thin eyebrows with flaring in their midline portion, a large nose with a high bridge and flared nostrils, M-shaped Cupid's bow, fleshy lips, and wide mouth with shallow and broad palate, dysplastic and thick ear helices, and full cheeks. She had a single palmar crease, small hands, and feet. Agitation, poor eye contact, stereotypic movements of the hands and the head were observed. In the ophthalmic examination, astigmatism was detected, retinal and fundus examinations were normal. Mild hypotonia persisted.

Routine biochemical examinations and metabolic studies such as ammonia, ceruloplasmin, homocysteine, folic acid, vitamin B12, thyroid function tests, plasma amino acid analysis were within normal limits. Conventional cytogenetic analysis, FISH analysis for AS, and Prader-Willi (PWS)/AS-specific methylation analyses were normal. By CES analysis, we detected a heterozygous c.1113delC variant in the TCF4 gene which was classified as pathogenic according to the ACMG variant interpretation guideline. The patient was diagnosed with Pitt Hopkins syndrome (OMIM: 610954) with this variant.

Case 3

The third patient was a 7-year-old boy, who was born 820 gr in the 24th gestational week from consanguineous parents. He had intracranial hemorrhage at birth and stayed in NICU for 4 months. He received mechanical ventilator support. He had apnea and breath-holding spells during his NICU stay. He had hypotonia and microcephaly during the first year of his life. He had a psychomotor developmental delay. He was unable to raise his head until age of 12 months. He was able to walk at age 6 years, but walking was unsteady and ataxic. Speech development was absent. He had a constipation complaint at age 1 year. At the age 4 years, several episodes of hyperventilation were observed. He was checked and treated for retinopathy of prematurity (ROP).

Physical examination showed short neck and typical facial dysmorphism; heavy supraorbital regions, a broad and beaked nose with a high bridge and flaring nostrils, a wide mouth, a bow-shaped upper lip, broad palate, widely spaced teeth, dysplastic and thick ear helices, and protruding lower face, and micropenis. He had clubbing fingers, small hands, and feet. In the ophthalmic examination, astigmatism was detected, retinal and fundus examinations were normal. He suffered from chronic constipation. He showed autistic features such as low frustration tolerance, sleep disturbances, stereotypical hand and head movements, and poor eye contact. His full-scale intelligence quotient (IQ, Stanford Binet Intelligence Scales, 5th Edition) was 57.

Routine biochemical examinations and metabolic studies such as ammonia, plasma, and urine amino acid analysis, long-chained fatty acid analysis, urine organic acid analysis, and tandem mass spectrometry were within normal limits. Abdominal ultrasounds, echocardiography, MR spectroscopy, EEG, and EMG were normal. His cranial MRI showed diffuse cerebellar atrophy. Conventional

cytogenetic analysis and FISH analysis for AS were normal. By whole-exome sequencing (WES) analysis, we detected a novel heterozygous c.611-180dupT variant in the TCF4 gene which was classified as pathogenic according to ACMG variant interpretation guideline. The patient was diagnosed with Pitt Hopkins syndrome (OMIM: 610954) with this variant.

Case 4

Patient four; was an 8-year-old girl, who was born 2750 gr, by cesarean section, from healthy, consanguineous parents. Her prenatal period was uneventful. During the first year of her life, severe psychomotor delay, and microcephaly were observed. She was able to raise her head at 3 months and sit unsupported at age 3 years. She was able to walk at age 4.5 years yet still she was unable to walk independently.

Speech development was absent. Urinary control had not developed. She had a long-standing history of constipation. She had never experienced apnea, breath-holding spells, or episodes of hyperventilation. She first presented to medical attention at the age 9 months, with hypotonia and developmental delay.

In physical examination, she had a short neck and typical facial dysmorphism; includes coarse face, bitemporal narrowing, thin eyebrows with flaring in their midline portion, peculiar nose conformation, with a broad nasal bridge, down-turned nasal tip, large nostrils, wide mouth, bow-shaped upper lip, broad palate, widely spaced teeth, dysplastic and thick ear helices, well-developed chin and protruding lower face. She had a smiling appearance. Anxiety behaviors and stereotypic movements of the hands (wringing and swaying) and the head were observed. Poor eye contact was noted. Her full-scale intelligence quotient (IQ, Stanford Binet Intelligence Scales, 5th Edition) was 62.

No abnormalities were detected in routine biochemical examinations and metabolic studies such as ammonia, plasma, and urine amino acid analysis, long-chained fatty acid analysis, urine organic acid analysis, and tandem mass spectrometry. She had congenital hypothyroidism. Ophthalmic examination was normal. Abdominal ultrasound, EEG, and EMG were normal as well. She had minimal ASD and VSD in echocardiography. Her cranial MRI showed corpus callosum agenesis.

Conventional cytogenetic analysis and FISH analysis for AS were normal. By WES analysis, a known pathogenic, heterozygous c.1459C>T variant in the TCF4 gene was detected, and the patient was diagnosed with Pitt Hopkins syndrome (OMIM: 610954) with this variant.

Case 5

The last patient was a 6-year-old girl, who was born 2900 gr, by cesarean section, from healthy, nonconsanguineous parents. Her prenatal period was uneventful. Her head circumference was less than 3 percentiles. During the first year of her life, severe psychomotor delay was observed. She was unable to raise her head until age of 12 months. She was able to walk at age 4 years, but she has been still walking unsteady and ataxic. Speech development was absent. She first presented to medical attention at age 3 months, with hypotonia and microcephaly. Apnea and breath-holding spells were observed but she had no seizures. She had a long-standing history of constipation.

In physical examination, she had a short neck and typical facial dysmorphism includes coarse face, full cheeks, flaring eyebrows, hypertelorism, broad nasal bridge, down-turned nasal tip and flaring nostrils, wide mouth, bow-shaped upper lip, broad palate, widely spaced teeth, dysplastic and thick ear helices. She had clubbing fingers, small hands, and feet.

Anxiety behaviors, stereotypic movements of the hands (hand clapping and flapping), and the head were observed. Ophthalmic examination was normal. Poor eye contact was noted. Her full-scale intelligence quotient (IQ, Stanford Binet Intelligence Scales, 5th Edition) was 53.

Routine biochemical examinations and metabolic studies such as ammonia, plasma, and urine amino acid analysis, long-chained fatty acid analysis, urine organic acid analysis, and tandem mass spectrometry were within normal limits. Abdominal ultrasounds, echocardiography, MR spectroscopy, and EMG were normal. Her cranial

MRI showed mild cerebellar atrophy and corpus callosum agenesis. EEG studies revealed focal temporal epileptic activity however she had no seizure. The patient was diagnosed with Pitt Hopkins syndrome at a different genetic testing center. Conventional cytogenetic analysis and FISH analysis for AS were normal. They detected a known pathogenic c.2039G>A variant in the TCF4 gene by using NGS panel for Mendelian diseases.

Figure-1: Facial features of the patients. Images are numbered in order as mentioned in the article. Coarse face, bitemporal narrowing, squared forehead, full cheek, broad nasal bridge, down-turned nasal tip and flaring nostrils, m shaped upper lip are seen in all patients. Patient 3 also has dysplastic and thick ear helices and protruding lower face.

DISCUSSION

PTHS is a rare, nonprogressive encephalopathy, characterized by distinct facial features, severe developmental delay with moderate-to-severe intellectual disability and behavioral disturbances, loss of speech, tendency to epilepsy, episodic hyperventilation, and/or breath-holding while awake, and a variety of additional clinical findings. PTHS is caused by haploinsufficiency of the TCF4 gene at 18q21.2 due to deletions, stop, splice-site, and de novo missense mutations [6]. TCF4 gene contributes to human development by regulating the expression of several genes. Therefore, apart from TCF4 gene mutations, changes in the function and expression of the genes controlled by TCF4 may also affect the phenotype of PTHS patients [7].

Characteristic facial features of PTHS contain bitemporal narrowing, full cheeks with a prominent lower face, deep-set eyes, large nasal bridge, large mouth with M-shaped upper lip, protruding and thick lower lip vermillion, cup-shaped ears, and widely spaced teeth. Sweet personality, subtle brain abnormalities, seizures, postnatal microcephaly, ataxic gait/motor incoordination, stereotypic movements, strabismus, myopia, and astigmatism were the most frequent additional clinical manifestations of PTHS. Breathing abnormalities are a prominent part of PTHS, could be seen as breath-holding spells or hyperventilation episodes.

The diagnosis of PTHS is based on the typical clinical presentation confirmed by molecular genetic methods. PTHS is clinically overlapping with other several neurodevelopmental disorders such as AS, Rett Syndrome, and MWS. Differential diagnosis is mainly based on clinical findings. Although AS has a characteristic EEG pattern, MRI and EEG studies do not suggest specific diagnostic leads for the mentioned syndromes [8]. AS mostly presents with unmotivated laughing episodes, seizures, and microcephaly. In addition, AS patients lack the typical facial features observed in PTHS. In MWS, Hirschsprung disease is seen in almost half of the cases and cardiac and urogenital (hypospadias) malformations are common which could be useful for differential diagnosis. Rett syndrome is a progressive encephalopathy, with a normal early development is followed by arrest and regression of motor and cognitive skills. Intractable epilepsy presents in many patients with Rett syndrome. Importantly, patients lack the facial characteristics associated with PTHS [6,9].

Genotype-phenotype correlation analyses led researchers to define a clinical score system for targeted genetic testing for PTHS. Whalen et al. and Marangi et al. defined different scoring systems. Both studies attributed most of the points to characteristic facial configurations. Absent speech, ataxic gait, hyperventilation, and strabismus were the other common signs in both scoring systems. The main aim is to detect patients who need TCF4 screening as a first choice [9,10].

With NGS technologies, the rates of diagnosis, detection of new genes, and mutations have increased. This increase allows for the development of follow-up and treatment protocols depending on the clinical heterogeneity resulting from different mutations. Therefore, comparing the clinical findings of patients with different mutations in the same gene can provide important information. Here, in this study, we shared the clinical findings of 5 Pitt-Hopkins patients with 4 different TCF4 mutations by comparing them with the findings reported in the literature.

Genetic analyses were performed for all of our patients, and we detected a novel variant in patients 1 and 3 that was not reported in the literature previously. In order to confirm our results, we checked the reading frames by using integrative genomics viewer (IGV) [5]. All obtained variants were classified by using the American College of Medical Genetics and Genomics guideline [4]. After that, we reviewed the literature for each variant that was found in our patients and compared our clinical findings with the reported patients' clinical findings. Patients 2,4 and 5 had mutations that were previously reported.

Case 1 and 3 were diagnosed in our center and had the same variant in the TCF4 gene that had been not reported in the literature before. They shared several clinical features including hypotonia, developmental delay, absent speech, autistic features, stereotypic movements, poor eye contact, ocular findings, and dysmorphic features as shown in Table 1. Unlike Case 1, Case 3 had prematurity with intracranial hemorrhage and ROP, intellectual disability, and cerebellar atrophy. Both TCF4 gene mutation, and prematurity and intracranial hemorrhages at birth can cause intellectual disability and atrophy. As far as we know, a male patient with a preterm labor complication was reported in the literature, however, the patient's mutation was affecting another domain of the protein [11]. Therefore, the relationship between TCF4 gene mutation and preterm birth remains unclear. (Table 1)

Case 2 had TCF4 c.1113delC variant and classic features of Pitt-Hopkins syndrome. In the literature, only a VarSome user from Turkey reported this variant as disease-causing, but clinical findings of the patient were unavailable [12]. So, we could not compare the patients' clinical findings.

Case 4 had c.1459C>T variant in the TCF4 gene and Case 5 had c.2039G>A variant in the TCF4 gene, both had similar findings with the previously reported patients, and additionally, patient 4 had congenital hypothyroidism and urinary incontinence. The comparisons of clinical findings with the literature are shown in Table 2 and Table 3, respectively [13–16].

Limitations of the study

Our study has several limitations mainly related to the study population size The number of patients meeting the inclusion criteria was small because it was a single center study. However, this present study may contribute to national data and/or the systematic reviews and meta-analyzes [17] which will be done together with other studies originating from our country. In our opinion, It would be more effective to identify new variants and define the phenotype-genotype characteristics of these variants in a multi-center study.

CONCLUSION

Pitt-Hopkins syndrome should be considered in children with specific craniofacial dysmorphism, severe developmental delay, intellectual disability, breathing abnormalities, and disturbances of intestinal motility. The diagnosis of PTHS is a clinical one; clinical evaluation and genetic confirmation must be performed together. It is well known that a certain degree of genetic heterogeneity exists for well-defined clinical conditions, including PTHS. Therefore, more studies about genotype-phenotype correlations and novel variant reports are needed to make a precise diagnosis.

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Table 1: Comparison of clinical findings of TCF4 novel c.611-80dup variant

		Physical exam	Developmental exam	Radiologic/Ophthalmologic exam	Other
Present study	Case 1	•Coarse face •Bitemporal narrowing •Squared forehead •Full cheeks •Peculiar nose conformation, broad nasal bridge, down-turned nasal tip and flaring nostrils •M shaped upper lip •Short neck •Small hands and feet •Pes planus •Clinodactyly	•Psychomotor delay •Hypotonia •Absent speech •Autistic features •Stereotypic movements •Poor eye contact	•Strabismus	-
	Case 3	•Microcephaly •Heavy supraorbital regions •Dysplastic and thick ear helices •Protruding lower face •Broad and beaked nose with high bridge and flaring nostrils •Wide mouth, bow-shaped upper lip •Broad palate •Widely spaced teeth •Short neck •Clubbing fingers •Small hands and feet •Micropenis	•Psychomotor delay •Hypotonia •Absent speech •Intellectual disability •Autistic features •Stereotypic movements •Poor eye contact	•Astigmatism •Diffuse cerebellar atrophy	•Prematurity •Intracranial hemorrhage at birth •ROP •Apnea •Constipation •Hyperventilation episodes
Literature review	N/A				

Table 2: Comparison of clinical findings of TCF4 c.1459C>T variant

		Physical exam	Developmental exam	Radiologic/Ophthalmologic exam	Other
Present study	Case 4	•Microcephaly •Coarse face •Bitemporal narrowing •Squared forehead •Full cheeks •Peculiar nose conformation, with a broad nasal bridge, down-turned nasal tip and flaring nostrils, •M shaped upper lip •Short neck •Small hands and feet •Pes planus •Clinodactyly	•Severe psychomotor delay •Ataxia •Hypotonia •Absent speech •Happy appearance •Stereotypic movements •Poor eye contact •Anxiety •Constipation	•Minimal ASD and VSD •Strabismus •Corpus callosum agenesis	•Congenital •Hypothyroidism •Urinary incontinence
Literature review	Zweier et al.	•Microcephaly •Short hands and feet •Hyperconvex nails •Bilateral supernumerary digital flexion crease on 3 and 4th fingers •Single palmar crease	•Severe psychomotor delay •Ataxia •Hypotonia •Absent speech •Episodes of hyperventilation-apnea •Unmotivated laughter episodes •Very anxious and auto aggressive behavior •Constipation	•Strabismus	•MRI N/A
	Hamdan et al. N/A				

Table 3: Comparison of clinical findings of TCF4 c.2039G>A variant

		Physical exam	Developmental exam	Radiologic/Ophthalmologic exam	Other
Present study	Case 5	•Coarse face •Bitemporal narrowing •Squared forehead •Full cheeks •Peculiar nose conformation, with a broad nasal bridge, down-turned nasal tip and flaring nostrils •M shaped upper lip •Short neck •Small hands and feet •Pes planus	•Microcephaly •Severe psychomotor delay •Intellectual disability •Hypotonia •Absent speech •Apnea and breath-holding spells •Constipation •Anxiety stereotypic movements •Poor eye contact	•Mild cerebellar atrophy and corpus callosum agenesis •Focal temporal epileptic activity without seizure	-
Literature review	Mary et al.	•Mildly fascial gestalt	•Microcephaly •Intellectual disability •Delayed walking •Absent speech •Hyperventilation/apnea •Happy appearance •Sleep disturbances	•Duane anomaly	•Headaches
	Zweier et al (a) P13	•Typical fascial gestalt •Single palmar crease	•Intellectual disability •Hypotonia •Happy appearance •Stereotypic movements		•No microcephaly •No ventilation anomalies •Inability to use hands •Fetal pads of toes •Cold hands and feet
	Zweier et al (a) P16 (total patient number: 6)	•Typical fascial gestalt (all patients) •Single palmar crease (in 4 patients)	•Severe intellectual disability (all patients) •Seizures (in 2 patients) •Hypotonia (all patients) •Ventilation anomalies (in 5 patients) •Happy appearance (all patients)	•Arachnoidal cyst	•No microcephaly (but other 4 patients had) •No constipation (but in 3 patients) •No scoliosis (but in 2 patients) •Recurrent ear infections •One patient had accessory nipple, and 2 patients had strabismus

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CASE REPORT

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Very Late and Subacute Right Ventricular Lead Perforation Presenting as Cardiac Tamponade

Kardiyak Tamponad ile Başvuran Çok Geç ve Subakut Sağ Ventriküler Lead Perforasyonu

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ABSTRACT

Ventricular lead perforation (VLP) is a rare and life-threatening complication of permanent pacemakers. Generally, VLP emerges in acute and subacute periods after cardiac electronic devices are implanted. Late VLP is unexpected and occurs less frequently. There is an uncertain approach to the treatment of VLPs. Collaboration with cardiovascular surgeons is recommended. Herein, we present two cases of cardiac perforations who were successfully managed. One of them was admitted with cardiac tamponade four years after dual-chamber pacemaker (DCP) implantation, and the right ventricular lead was successfully removed with an open surgical method. The other was admitted with cardiac tamponade two weeks after DCP implantation. Ventricular lead was extracted by a simple traction method without surgical support and successfully re-implanted in the correct location.

Keywords: Pacemaker, cardiac perforation, cardiac tamponade

ÖZ

Ventriküler lead perforasyonu (VLP), kalıcı kalp pillerinin nadir görülen ve hayatı tehdit eden bir komplikasyonudur. Genellikle VLP, kardiyak elektronik cihazlar implante edildikten sonra akut ve subakut dönemlerde ortaya çıkar. Geç VLP alışılmadık bir durumdur ve daha az sıklıkla meydana gelir. VLP'lerin tedavisine yönelik belirsiz bir yaklaşım vardır. Kardiyovasküler cerrahlarla işbirliği önerilir. Burada başarıyla tedavi edilen iki kardiyak perforasyon vakasını sunuyoruz. Bunlardan biri çift odacıklı kalp pili (DCP) implantasyonundan dört yıl sonra kalp tamponadı ile başvurdu ve sağ ventrikül lead'i açık cerrahi yöntemle başarıyla çıkarıldı. Diğeri, DCP implantasyonundan iki hafta sonra kardiyak tamponad ile kabul edildi. Ventriküler lead, cerrahi destek olmaksızın basit bir traksiyon yöntemiyle çıkarıldı ve doğru yere başarıyla yeniden implante edildi.

Anahtar kelimeler: Pacemaker, kardiyak perforasyon, kardiyak tamponad

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INTRODUCTION

Ventricular lead perforation (VLP) is a rare and severe complication encountered after permanent pacemaker implantation. Frequently, VLP provides symptoms in the early postoperative period. Late VLP is unusual. Patients may present with the asymptomatic or life-threatening condition of cardiac tamponade. [1] Management and treatment of VLP are controversial. Decisions by councils, which consists of cardiovascular surgeons and cardiologists, are essential for the management of ventricular perforations. [2]

We present two cases of cardiac perforation, which emerged four years and two weeks, respectively, after cardiac implantable electronic device (CIED) was inserted.

Case 1

An 81-year-old male patient was admitted to our clinic with shortness of breath. Electrocardiogram (ECG) showed complete heart block (CHB). He had a dual-chamber pacemaker (DCP) implanted in 2016 due to CHB (5076 capsurefix novus ventricular lead (VL), 5594 CapSure SP Novus atrial lead, values of origin VL were 659 ohms, sensing 8 V and threshold 1 V). Massive pericardial effusion and cardiac tamponade were evident in the echocardiography. Emergency percutaneous pericardial drainage was performed because of hemodynamic instability. Pericardial effusion had hemorrhagic character, and 700 ml effusion was drained. Additionally, the tip of the right VL was observed outside the ventricle on echocardiography (Figure 1A). A temporary pacemaker was implanted in the catheter laboratory. After hemodynamic stabilization, the patient underwent computed tomography (CT) assessment. The right VL tip was outside on CT (Figure 1B). Pace control revealed that the pacemaker was end of life, and the right VL was not pacing. When control records of the patient were examined, impedance and sensing values of the right VL were average at device interrogation one year previously. The remaining battery time was about three years. Extraction of VL was decided by open surgery because the patient was admitted with clinical findings of cardiac tamponade four years after CIED. Median sternotomy was performed in the hybrid operating room, and we successfully removed VL by a simple traction method. The ventricular perforation area was repaired with simple suturing (Figure 1C). Then, a new right VL and battery were placed in the same session. The patient was discharged uneventfully five days after the operation.

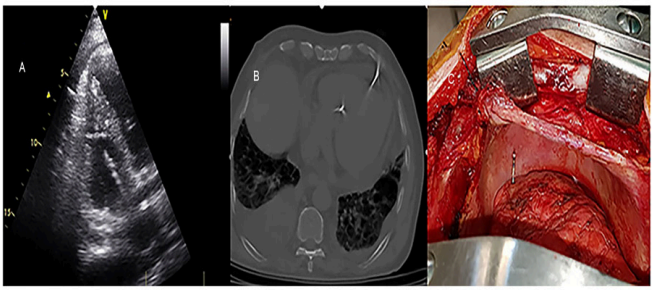

Figure 1. A. Ventricular lead tip outside of the right ventricular cavity on echocardiographic assessment. B. Chest computed tomography depicting lead perforation. C. Surgical view showing the perforating lead

Case 2

A 60-year-old female patient was admitted to the emergency service with complaints of shortness of breath and dizziness. DCP (Tendril 5088-58 VL, Tendril 5058-52 atrial lead) was implanted two weeks previously. ECG showed low voltage. Cardiac tamponade was identified on echocardiography, and VLP was observed on thorax CT (figure 2). Intracardiac records show that right ventricle (RV) impedance was higher than onset impedance values, and RV threshold had minimally increased (RV impedance 1004 ohms, origin impedance 759 ohms, RV threshold 3V, origin threshold 0.8 V). Emergency pericardial drainage was performed. Pacemaker lead revision was performed by the simple traction method, and the same lead was implanted in the proper localization under surgeon observation. She was discharged uneventfully three days after the lead revision.

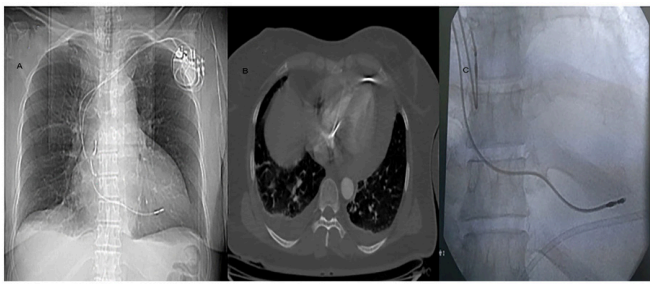

Figure 2. A. Chest X-ray depicting right ventricular lead outside the cardiac border B. Thorax CT showing right ventricular lead perforation C. Angiographic image demonstrating right ventricle lead tip outside the cardiac silhouette

DISCUSSION

Various complications can occur in the early and late periods after implanting permanent pacemakers. Among the complications, local hemorrhage, inflammation in the pulse generator pocket, hemothorax, pneumothorax, cardiac perforations, atrial and ventricular lead dislodgment can be listed. These complications are diagnosed by radiological imaging methods (chest x-ray and CT), echocardiography, and any programmable output (failure to capture or sense or both). Treatment of complications generally requires invasive re-operation and a multidisciplinary approach by surgeons. [1]

Ventricular lead perforations are life-threatening complications. Generally, VLPs are diagnosed in acute and subacute periods. Most patients are admitted with shortness of breath and stabbing chest pain. Tamponade and severe pericardial effusion are observed less than excepted. Perforation of the liver lobe, chest muscle twitching, hiccups, and chest wall hematoma due to the migration of the lead were rarely reported in previous studies. When the lead migrates out of the cardiac silhouette, echocardiography, fluoroscopy, and chest radiography can detect the problem. Sometimes cardiac perforation may develop after many years without any symptoms. Late lead perforations are very rare in the literature. [3] Cano et al. reported that cardiac perforation was detected in 17 (13 acute and 4 subacute perforations) (0.8%) of 3822 active pacemaker patients. Thirteen patients had pericardiocentesis performed and late VLP was not observed in this study. Female gender, apically localized lead, and age over 80 years were risk factors for VLP. [4]

Active ventricular fixation leads are usually used in CIED. Active fixation leads are responsible for cardiac perforations. Sterlinski et al. compared actively and passively fixated VLs with active fixation performed in 1,200 patients and passive fixation in 1047 patients. Cardiac perforation occurred in eight patients. All of them were associated with active fixation lead implantation. [5] Helical screw active fixation was used in our two cases. The second case presented with cardiac tamponade in the early period. The tip of the lead was outside of the heart on imaging so we can understand why symptoms emerged in the subacute period. The first case did not have any symptoms for a long time, neither during pacemaker checks nor on imaging. The screw of the lead likely passed into the pericardium, not the whole lead tip. Each ventricular contraction may cause the progression of the lead and deteriorate the myocardium. This can explain causing cardiac tamponade for an extended period.

There are few cases of late VLP in the literature. Ventricular leads which were implanted for more than one year can be removed by the transvenous lead extraction method or surgical method. Surgical removal is infrequent. Surgical removal is performed when there are concomitant conditions such as cardiac tamponade, tricuspid valve endocarditis, or valve stenosis and undergoing coronary artery bypass graft. [6] We decided to surgically remove VL due to the possibility of active bleeding related to long implantation time and defect of the ventricle in the first patient. Median sternotomy was performed to repair the bleeding focus and exclude causes of hemorrhagic effusion in our first case. In a study consisting of 14 patients, lead extraction was performed using minimal surgical procedures. A minimally invasive method was performed due to infective endocarditis and lead malposition. [7] Cardiac perforation and tamponade were not stated in this study. The second case presented with cardiac tamponade in the subacute period. But this patient didn't undergo a surgical operation. Hitochi et al. retrospectively studied 1359 patients with CIED. Fifteen patients had VLP in the early period. The ventricular lead was withdrawn and re-implanted in 14 patients without a surgical method. [2] No complications were observed. VL extractions without surgical techniques are uncommon in patients who present with cardiac tamponade. The transvenous extraction method was successfully performed, and ventricular lead was re-implanted in our second case without any complications during 6 months of follow-up. It is likely the reason was low right pressure, myocardial contraction, and covering perforation with fibrosis.

CONCLUSION

Management of VLP is complicated and difficult. Extraction of right VL by the surgical method

may be appropriate in terms of complications, but VL which is responsible for perforation can be extracted by the simple traction method under X-ray in acute and subacute VLP. We rarely encounter VLP causing cardiac tamponade even after many years. The RV can be repaired by the surgical method due to bleeding risk.

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