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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratio Values in Patients with Ischemic Stroke in Terms of Disease Severity Based on NIHSS

İskemik İnme Hastalarında Nötrofil/Lenfosit ile Platelet/Lenfosit Oranının NIHSS'e Göre Hastalık Prognoz Tahminindeki Yeri

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ABSTRACT

Aim: *Stroke is the most common neurological cause of morbidity and mortality worldwide. Therefore, controlling the risk factors in an early phase is critically important. In this study, we aimed to investigate the advantages of neutrophile lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) values against each other in predicting the prognosis of ischemic stroke.*

Material and Method: *143 ischemic stroke patients were included in to study. Blood sample analysis was done to calculate NLR and PLR. Patients' NIHSS at first admission was also calculated. Multiple statistical analyses were used to analyze the statistical significance of NLR and PLR's predictive power in poor prognosis.*

Results: *We found that NLR was lower in those with a stroke scale score of 5 and below; the difference was statistically significant (p=0.015). The results of the ROC curve analysis showed that the NLR value was statistically significant in predicting patients categorized as NIHSS 6 and above (p<0.001).*

Conclusion: *This study is one of the first in the literature to evaluate the advantages of NLR and PLR values against one another in predicting stroke prognosis. Results show that the NLR value has a higher statistical significance in predicting prognosis than the PLR value. It is believed that prospective randomized studies can draw more meaningful conclusions on a larger set of patients.*

Key words: *stroke scale; neutrophil/lymphocyte ratio; ischemic stroke; platelet/lymphocyte ratio; prognosis; cerebrovascular disorders*

ÖZET

Amaç: *İnme, dünyadaki morbidite ve mortalitenin en yaygın nörolojik nedenidir. Bu nedenle risk faktörlerini erken bir aşamada kontrol etmek kritik derecede önemlidir. Bu çalışmada, nötrofil lenfosit oranı (NLO) ve platelet lenfosit oranı (PLO) değerlerinin iskemik inme prognozunu öngörmede birbirlerine olan avantajlarını araştırmayı amaçladık.*

Materyal ve Metot: *Çalışmaya 143 iskemik inme hastası dahil edildi. NLO ve PLO değerini hesaplamak için kan örneği analizi yapıldı. Hastaların ilk başvurudaki NIHSS değeri hesaplandı. NLO'nin istatistiksel önemini ve kötü prognozda PLR'nin öngörü gücünü analiz etmek için çoklu istatistiksel analiz kullanıldı.*

Bulgular: *İnme ölçeği puanı 5 ve altında olanlarda NLO'nun daha düşük olduğu tespit edildi, aradaki fark istatistiksel olarak anlamlı bulundu (p=0,015). ROC eğri analizi sonuçları, NIHSS 6 ve üstü olarak kategorize edilen hastaları tahmin etmede NLR değerinin istatistiksel olarak anlamlı olduğu saptandı. (p<0,001).*

Sonuç: *Bu çalışma, inme prognozunu öngörmede NLO ve PLO değerlerinin birbirine göre avantajlarını değerlendiren literatürdeki ilk çalışmalardan biridir. Sonuçlar, NLO değerinin, PLO değerine kıyasla prognozu tahmin etmede daha yüksek bir istatistiksel öneme sahip olduğunu göstermektedir. Daha geniş hasta grubunda ileriye dönük randomize çalışmalarla daha anlamlı sonuçların çıkarılabileceğine inanılmaktadır.*

Anahtar kelimeler: *inme ölçeği; nötrofil/lenfosit oranı; iskemik inme; trombosit/lenfosit oranı; prognoz; serebrovasküler bozukluklar*

Introduction

A stroke is a neurological deficit after focal vascular damage to the central nervous system. Stroke is the most common neurological cause of morbidity and mortality in the world[1]. Therefore, it is critically important to understand all the factors involved in the development of stroke and to control the risk factors in an early phase[1]. Prognostic evaluation is important in choosing treatment but remains a serious challenge for clinicians. Therefore, it is important to find low-cost

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and inclusive factors to evaluate stroke prognosis[2]. The inflammatory response has been shown to contribute to all pathophysiological processes in acute ischemic stroke[1]. Neutrophils and lymphocytes play an important role in regulating the immune response to cerebrovascular disease. An increase in white blood cells and neutrophils in patients with acute ischemic stroke in early stages has been associated with larger infarct volumes and an increased risk of stroke[1]. On the other hand, a decrease in lymphocyte count has been associated with poor functionalities in the three months after acute ischemic stroke.

The platelet-to-lymphocyte ratio (PLR) was an important marker of atherosclerosis's inflammation and severity of atherosclerosis[3]. In a study, the blood PLR value was significantly increased in patients with transient ischemic attack and stroke compared to the control group[4].

In this study, we aimed to investigate the advantages of neutrophil-lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) values against each other in predicting the prognosis of ischemic stroke.

Methods

Population Selection

We retrospectively evaluated the records of 257 consecutive ischemic stroke patients hospitalized in Kars Harakani state hospital from 2014 to 2016. Patients with hematological disease, history of cancer, severe renal and hepatic insufficiency, and a history of infection starting within 72 hours from the onset of stroke symptoms were excluded from the assessment. Patients with a brain stem, cerebellar, and acute hemorrhagic stroke wherein the effect of NLR and PLR values on the prognosis could not be examined and which could seriously affect the prognosis were also excluded. Also, patients receiving antibiotics, immunosuppressive therapy, and non-steroidal anti-inflammatory drugs were excluded from the study. Three patients were not evaluated due to lack of data, and seven were due to pneumonia during the stroke. Thus, a total of 143 patients were included in the study.

Studying Protocol

Electronic records of patients hospitalized for ischemic stroke were scanned from the hospital's electronic database system. Patients who developed stroke symptoms in the last 72 hours were selected. Patients' demographic and clinical characteristics were evaluated according to the National Institutes of Health Stroke Scale (NIHSS). NIHSS five and below were described as minor stroke and NIHSS six and above as severe stroke.

Chronic diseases of the patients were listed as hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, and hyperlipidemia.

Analysis of Blood Samples

Complete blood count tests were performed using the patients' first peripheral venous blood samples within the admission date. When calculating NLR and PLR, the arithmetic mean was calculated based on the individual numerical values of lymphocyte, neutrophil, and platelet values.

Statistical Analysis

Patients' data were entered into the SPSS 20.0 program, and statistical analysis was done with r 3.3.2v (open source) program. In statistical analyses, the significance level was set at $p<0.05$. Categorical variables were summarized as numbers and percentages. Spearman Rho correlation coefficient was used to examine the associations between numerical variables. The normality of numerical variables was checked with Kolmogorov–Smirnov test. NIHSS cut-off values were taken as five and below for mild stroke and six and above for severe stroke. Mann-Whitney U method was used to check whether there was a significant difference between NLR and PLR considering the demographic characteristics of the patients and to investigate the significant variability of blood NLR and PLR values according to the cut-off value of the patients' stroke scale (NIHSS) scores at first admission. ROC curve analysis was performed to assess the significance of predicting morbidity between NLR and PLR in terms of sensitivity and specificity based on the cut-off value.

Results

Basic Characteristics

Sixty-six patients (47.83%) were male, and 77 (52.17%) were female. 23 patients (16.7%) had diabetes, 75 (54.35%) hypertension, 39 (28.68%) atrial fibrillation, 16 (11.68%) coronary artery disease, and 13 (21.67%) hyperlipidemia. Stroke scale score was five and below in 48.91% of the patients, six and above in 51.09%.

NLR value was 2.7 (2.03–4.38) in males, and 2.71 (1.8–4.68) in females, with no significant difference between them (p=0.771). PLR value was 133.665 (106.94–199.1) in males and 135.64 (104.28–186.85) in females, with no statistically significant difference (p=0.998).

NLR value was 2.750 (1.84–4.83) in patients with diabetes and 2.705 (1.96–4.33) in patients without diabetes; the difference between medians was not found statistically significant (p=0.831). The PLR value was 132.76 (95.23–176.72) in patients with diabetes, and 136.23 (106.94–197.72) in patients without diabetes, with no significant difference between medians (p=0.484).

There was no difference between NLR and PLR (p>0.05) depending on whether or not patients had hypertension, atrial fibrillation, coronary artery disease, and hyperlipidemia (Table 1).

Correlation Between Stroke Severity and NLR-PLR Value:

We investigated for any significant difference between patients' blood NLR and PLR values by their stroke scale scores at first admission. We found that the neutrophil/lymphocyte ratio was lower in those with a stroke scale score of five and below (2.26 (1.74–4.19)) as compared to those with a score of six and above (3.18 (2.11–5.25)); the difference was found to be statistically significant (p=0.015). On the other hand, the platelet/lymphocyte ratio was lower in those with a stroke scale score of five and below (130.18 (104.91–186.2)) as compared to those with a score of six and above (138.595 (100.75–193.1)), with no statistically significant difference between them (p=0.490).

ROC Analysis

The results of the ROC curve analysis showed that, according to the AUC (area under the curve) value of the NL variable, the NLR value was statistically significant in predicting patients categorized as NIHSS six and above (p<0.001) (Fig. 1). The ROC curve, sensitivity, and specificity values for the NLR value are below. Youden's index is calculated as J=sensitivity + specificity - 1 and takes a value in the range of (-1, +1). When Youden's index J is less than zero, the test has no diagnostic value. The correlation criterion can be determined based on where the Youden index value is maximal. Accordingly, the correlation criterion was set at ≤2.7. The sensitivity value obtained for this value is 62.86%, and the specificity value is 62.69%.

Table 1. *Comparison of Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratios by gender, Diabetes, Hypertension, Atrial Fibrillation, Coronary Artery Disease, Hyperlipidemia, and Stroke Scale Status*

	Neutrophile/Lymphocyte	p	Platelet/Lymphocyte	P
Gender				
Men (n=66)	2.70 (2.03–4.38)	0.771	133.665 (106.94–199.1)	0.998
Women (n=72)	2.71 (1.8–4.68)		135.64 (104.28–186.85)	
Diabetes Mellitus				
Yes (n=23)	2.750 (1.84–4.83)	0.831	132.76 (95.23–176.72)	0.484
No (n=115)	2.705 (1.96–4.33)		136.23 (106.94–197.72)	
Hypertension				
Yes (n=75)	2.86 (1.85–4.83)	0.368	138.480 (110.26–199.1)	0.182
No (n=63)	2.495 (2–4.08)		128.825 (100.75–184.61)	
Atrial Fibrilation				
Yes (n=39)	2.88 (2.09–5.02)	0.447	122.915 (97.64–198.69)	0.404
No (n=97)	2.7 (1.85–4.33)		136.23 (110.89–188.11)	
Coronary Artery Disease				
Yes (n=16)	2.705 (1.635–4.55)	0.502	122.665 (79.01–156.65)	0.153
No (n=121)	2.725 (1.955–4.505)		137.28 (106.94–197.72)	
Hyperlipidemia				
Yes (n=13)	1.96 (1.71–4.38)	0.414	127.71 (115.42–197.72)	0.936
No (n=47)	2.88 (2.01–5.02)		134.48 (110.89–187.67)	
NIHSS*				
5 and below (n=65)	2.26 (1.74–4.19)	0.015*	130.18 (104.91–186.2)	0.490
6 and over (n=70)	3.18 (2.11–5.25)		138.595 (100.75–193.1)	

*: p<0.05 Mann-Whitney U test *Stroke Scale

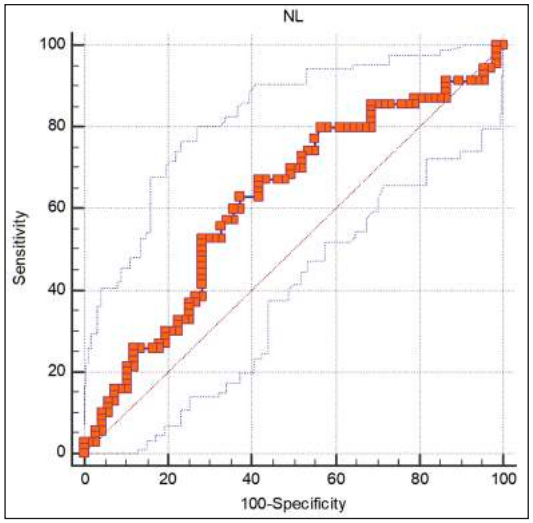

Figure 1. *NLR predictive value.*

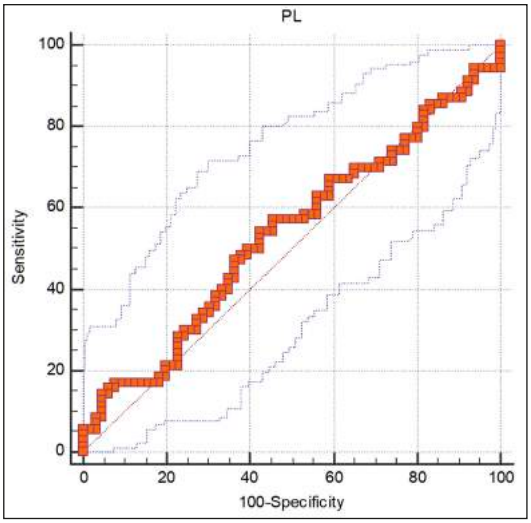

Figure 2. *PLR predictive value.*

The results of the ROC curve analysis showed that according to the AUC (area under the curve) value of the PL variable, the PLR value was not found to be statistically significant in predicting patients categorized as NIHSS six and above (p=0.4914) (Fig. 2).

In predicting the poor prognosis based on NIHSS score in an ischemic cerebrovascular accident, the optimal cut-off value according to the ROC curve was 2.7 for NLR and 136.23 for PLR.

Discussion

This study is one of the first in the literature to evaluate the advantages of NLR and PLR values against one another in predicting stroke prognosis. Results show that the NLR value has a higher statistical significance in predicting prognosis than the PLR value.

The main limitation of our study is that it is retrospective and has a limited number of patients.

Neutrophil and lymphocyte cells play an important role in the development of atherosclerosis. Neutrophils increase atherosclerosis through inflammatory reaction, protein hydrolysis, and oxygen stress reaction. Lymphopenia is also responsible for the development of atherosclerosis. Another possible mechanism is that the NLR value can reflect the autonomic nervous system[5]. Neutrophils have adrenergic receptors and are stimulated by sympathetic fibers. Lymphocytes have cholinergic receptors, and the lymphocyte function is regulated by parasympathetic nerves[5]. The role of lymphocytes in ischemic stroke is controversial. They are reported not only to have healing and repair effects but also to worsen the ischemic accident as they are a proinflammatory source of cytokines[1].

Recent studies have shown that the blood NLR value is statistically significantly associated with mortality in patients with acute ischemic stroke. A high NLR value at first admission to the hospital is associated with mortality from acute ischemic stroke in the first 60 days[6].

It is also suggested that basal neutrophil values are associated with the severity of tissue damage in ischemic stroke, the risk of stroke recurrence, and poor neurological consequences[4]. A study found markedly increased levels of blood neutrophils in patients with lacunar stroke, demonstrating a significant relationship between the level of neutrophils and the size of the stroke area independently from etiology[4]. In another study, blood NLR, eosinophils, and RDW values were identified as independent factors indicating the prognosis for ischemic stroke[3]. Given these studies, it makes sense that the NLR value also stands out in determining the prognosis in our study. In addition to chronic inflammation in the relationship between increased NLR and ischemic stroke, conditions related to increased neutrophil activity, such as the formation of neutrophil extracellular traps, may also be associated with thrombosis[7].

In another study, NLR was found to be higher in patients with poor prognosis according to Modified Rankin Scale (MRS)[8]. Similarly, in our study, the NLR value was significantly higher in patients with poor

prognoses (NIHSS >6) at first hospitalization. This picture can also be considered as a criterion for measuring morbidity. Similarly, it is suggested in a study that a high level of NLR presented the highest risk of unfavorable functional outcomes like ours[11].

PLR is of high prognostic value in terms of showing inflammatory destruction in cardiovascular diseases. It plays an important role in plaques' development, destabilization, and rupture. The decrease in the total and relative number of lymphocytes circulating in the blood is due to the increased production of cortisol caused by physiological stress. Therefore, high levels of platelet and low levels of lymphocytes can be associated with poor prognosis in ischemic accidents[9]. Moreover, a study found a markedly negative correlation between mortality and blood lymphocyte levels after ischemic stroke, indicating there may be a correlation between lymphopenia and the severity of stroke[4]. Sixteen studies were included in a systematic review and nine in the meta-analysis. On analysis of eight studies, there was no statistically significant relationship between PLR and poor functional outcomes in patients with stroke[12].

In our study, the PLR was found to be higher in patients with NIHSS six and above than in patients with NIHSS five and below, but the difference was insignificant.

Routine hematological measurements are superior to other blood markers because they are easily accessible, low-cost, objective, and therefore easily preferable in clinical practice[2].

In conclusion, it was found that the NLR value may be superior to the PLR value in determining the prognosis of ischemic stroke patients and planning treatment strategies. It is believed that prospective randomized studies can draw more meaningful conclusions on a larger set of patients.

Declarations of Interest

None

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Relationship Between Well-Being, Psychological Resilience, and Life Satisfaction of Residents

Asistan Hekimlerin İyi Olma Hali, Psikolojik Dayanıklılığı ve Yaşam Doyumları Arasındaki İlişki

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ABSTRACT

Aim: *In this study, the objective was to compare the psychological well-being, psychological resilience, and life satisfaction of the resident physicians working in our hospital according to their gender and branches.*

Material and Method: *"Personal Information Form", "Brief Psychological Resilience Scale", "Psychological Well-Being Scale" and "Life Satisfaction Scale" were used as data collection tools to evaluate the socio-demographic qualities of the resident physicians. The results and study data obtained were analyzed using the SPSS 22 program.*

Results: *Psychological resilience, psychological well-being, and life satisfaction did not differ according to the resident's gender. While the psychological resilience of resident physicians did not differ statistically according to their branches, the psychological well-being and life satisfaction of the resident physicians working in internal medical science were higher than of other resident physicians. No statistically significant difference was found in the psychological well-being and life satisfaction of the resident physicians working in the Surgical Medical Science and emergency department.*

Conclusion: *It was found that psychological resilience did not differ according to the branches of the resident physicians. However, the psychological well-being and life satisfaction of physicians working in internal medical science were higher than those working in surgical medical science. At the end of the study, the Life satisfaction of emergency medicine, which is regarded as one of the internal medical science, was closer to scores of the surgical medical science.*

Key words: *psychological well-being; life satisfaction; psychological resilience*

ÖZET

Amaç: *Bu çalışmada hastanemizde çalışan asistan hekimlerin psikolojik iyi olma hali, psikolojik dayanıklılıkları ve yaşam doyumlarının cinsiyet ve branşlarına göre karşılaştırılması amaçlandı.*

Materyal ve Metot: *Asistan hekimlerin sosyo-demografik özelliklerini değerlendiren "Kişisel Bilgi Formu", "Kısa Psikolojik Sağlamlık Ölçeği", "Psikolojik İyi Olma Ölçeği" ve "Yaşam Doyumu Ölçeği" veri toplama araçları olarak kullanıldı. Çalışmamızda elde edilen sonuçlar ve çalışma verileri SPSS 22 programı kullanılarak analiz edildi.*

Bulgular: *Cinsiyetlerine göre psikolojik sağlamlık, psikolojik iyi olma ve yaşam doyumları farklılık göstermedi. Branşlarına göre asistan hekimlerin psikolojik sağlamlıkları istatiksel olarak anlamlı farklılık göstermez iken dâhili branşlarda çalışan asistan hekimlerin psikolojik iyi olma halleri ve yaşam doyumları diğer asistan hekimlerden daha yüksek bulundu. Cerrahi branşlar ile acil tıp kliniğinde çalışan asistan hekimlerin psikolojik iyi oluşları ve yaşam doyumlarında istatiksel olarak anlamlı farklılık tespit edilmedi.*

Sonuç: *Asistan hekimlerin branşlarına göre psikolojik sağlamlığın farklılaşmadığı tespit edildi. Ancak dâhili branşlarda çalışan hekimlerin psikolojik iyi oluş ve yaşam doyumu cerrahi branşlarda çalışanlara göre daha yüksektir. Çalışmanın sonucunda dâhili branşlardan biri olarak kabul edilen acil tıbbın yaşam doyumu puanı cerrahi branşlara daha yakın bulundu.*

Anahtar kelimeler: *psikolojik iyi oluş; yaşam doyumu; psikolojik sağlamlık*

Introduction

Specialization training in medicine is a full-time training program conducted under supervision[1]. Doctors spend 3 to 7 years of their young adulthood in specialization training[2]. This period is a difficult one in that it creates a heavy burden for individuals. Stress is a condition inherent in the medical education process. Several types of research highlight the relationship between medical education and stress[3]. The specialty training

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process has also been related to anxiety, depression, loss of self, and emotional decline. All these events affect people's behavior and plans for the future. Several factors such as working hours longer and more than expected and promised, insufficient financial resources, isolation from the social environment, friends, relatives, and even family, and restriction of the time these physicians can spare for themselves pose a source of stress during specialty education[4]. It is also known that residents undergo much stress during this process, and this stress adversely affects the quality of health care[1].

In this study, the aim was to compare the well-being, psychological resilience, and life satisfaction of the resident physicians working in emergency medicine and internal and surgical medical science based on their gender and branches.

Materials and Methods

The universe of the study is comprised of the resident physicians working in the emergency department, and the internal and surgical medical science in a 3rd level education and research hospital in the 2018–2019 academic year. The study started after the approval of the ethics committee was taken. This hospital has 209 residents, 112 of whom work in internal medical science, 71 work in surgical medical science, and 26 work in the emergency department. 89.5% (n: 187) of these resident physicians participated in the study. It was stated that the answers given to the questions in the scales used in the study were based on the principle of volunteering and that they could act freely in the choice of whether to participate or not. The physicians participating in the research were told about the objective, quality, and requirements of the research. Resident physicians who did not want to participate in the study were not included.

Data Collection

In the study, a "Personal Information Form," "Brief Psychological Resilience Scale", "Psychological Well-Being Scale," and "Satisfaction Scale" were used as data collection tools to evaluate the socio-demographic qualities of resident physicians. Personal Information Form is a form consisting of a total of 14 questions to evaluate several features of resident physicians (age, gender, branch, place of duty, whether they have previously received specialty training, marital status, chronic illness, etc.). The Brief Psychological Resilience Scale (BPRS) we used in the study was developed by Smith et al. (2008)[5] and adapted to Turkish by Doğan (2015)[6]. The aim of using this scale was to evaluate the recuperation of residents, their getting better again and returning to their previous functional state, and their adaptability. Our scale is a tool that includes six questions that physicians answer about themselves and is a 5-point Likert type evaluation in which the scores go from 1 to 5. A person's high score based on his/her answers shows that his/her psychological resilience level is also high. The second psychological well-being scale (PWBS), which we used, was developed by Diener et al. (2009)[7] and was adapted to Turkish by Telef (2013)[8]. The scale is a 7-point Likert-type scale consisting of eight items. The scoring goes from 1 to 7 for each item. The statement "Strongly disagree" on the scale gets "1" as a score, and the statement "I strongly agree" gets seven as a score. It is stated that the higher the score is, the higher the psychological resources and resilience of the individual are. The Satisfaction with Life Scale (SWLS), developed by Diener, Emmons, Larsen, and Griffin in 1985 to evaluate life satisfaction, was used in the study[9]. The scale is a self-report scale consisting of five items assessing life satisfaction, using a 7-point Likert-type scoring system for each item. The scoring of the items in the scale goes thus: (1) is "not suitable," (7) is "very suitable." The high score obtained through the self-report of the individuals on the scale indicates that their satisfaction with life is also high.

Data Analysis

Categorical variables such as demographic data and descriptive characteristics of resident physicians were summarized as number (n) and percentage (%). Descriptive statics associated with continuous variables were shown as mean ± standard deviation. The normal distribution of the variables was measured with the Shapiro-Wilk test. The Student-t-test was used to compare normally distributed continuous variables, and the Mann-Whitney U-test was used to compare non-normally distributed samples. Chi-square (χ^2) test was used to compare categorical variables. One Way Anova test was used to compare the means of the three groups. Bonferroni's test was used as the Post Hoc test to determine the difference between the groups. In our study, SPSS 22 package program was used in the statistical evaluation of the data obtained (SPSS Inc, Chicago, Illinois, USA). As the statistical significance level, $p<0.05$ value was taken.

Results

A total of 187 resident physicians working in the emergency department, and internal and surgical medical science participated in the study. 38% (n: 71)

of the resident physicians participating in the study were female, 62% (n: 116) were male, and the mean age was 30.06±5.4 years. While the lowest resident physician age was 24, the highest was 53. The mean age of male residents was 30.65±6, and the mean age of female residents was 29.11±4.3. There was no statistically significant difference in the mean age of the physicians according to their gender (p=0.43). 48.1% (n: 90) of residents were married, 51.3% (n: 96) were single, 0.5% (n: 1) were divorced. 48.1% (n: 90) of residents were married, 51.3% (n: 96) were single, 0.5% (n: 1) were divorced. No statistically significant difference was observed between marital status and gender (respectively; 1.000, 0.881, and 1.000). A statistically significant difference was found between gender and branch groups (Emergency medicine, internal and surgical medical science) (respectively; 0.015, 0.001, 0.001). Male residents work in emergency medicine and surgery, and female residents mostly work in internal medical science. The relationship between gender and branches is presented in Table 1. It was found that the psychological resilience scores of resident physicians did not differ statistically according to their gender (p=0.253) and marital status (p=0.086). It was found that the psychological well-being scores of resident physicians did not differ significantly according to their gender (p=0.711) and their marital status (p=0.415). It is observed that the life satisfaction scores of resident physicians do not differ significantly according to their gender (p=0.191) and their marital status (p=0.380). Distribution of physicians between their gender and marital status, branches, group, and scores are summarized in Table 1.

Table 1. *Distribution of physicians between their gender and marital status, branches, branches group, and scores*

	Total N (%)	Male n: 116 (62%)	Female n: 71 (38%)	p
Age (years)	30.06±5.4	30.65±6	29.11±4.3	0.43
Marital Status				
Married	90 (48.1%)	56 (62.5%)	34 (37.8%)	1.000
Single	96 (51.3%)	59 (61.5%)	37 (38.5%)	0.881
Divorced	1 (0.5%)	1 (100%)	0 (0%)	1.000
Branches Group				
Emergency Medicine	26 (13.9%)	22 (84.6%)	4 (15.4%)	0.015
Internal Medical Science	107 (57.2%)	50 (46.7%)	57 (53.3%)	0.001
Surgical Medical Science	54 (28.9%)	44 (81.5%)	10 (18.5%)	0.001
Branches				
Emergency Medicine	26 (13.9%)	22 (84.6%)	4 (15.4%)	0.015
Internal Medicine	21 (11.2%)	12 (57.1%)	9 (42.9%)	0.639
Family Medicine	41 (21.9%)	19 (46.3%)	22 (53.7%)	0.028
Pediatrics	30 (16%)	8 (26.7%)	22 (73.3%)	0.001
Radiology	8 (4.3%)	7 (87.5%)	1 (12.5%)	0.263
Cardiology	7 (3.7%)	4 (57.1%)	3 (42.9%)	1.000
Orthopedics and Traumatology	12 (16%)	12 (100%)	0 (0%)	0.004
General surgeron	9 (4.8%)	9 (100%)	0 (0%)	0.014
Gynecology and Obstetrics	7 (3.7%)	2 (28.6%)	5 (71.4%)	0.107
Ophthalmologist	7 (3.7%)	6 (85.7%)	1 (14.3%)	0.256
Urology	6 (3.2%)	6 (100%)	0 (% 0)	0.084
Otolaryngology	5 (2.7%)	4 (80%)	1 (20%)	0.651
Neurosurgeon	4 (2.1%)	3 (75%)	1 (25%)	1.000
Cardiovascular Surgeon	3 (1.6%)	2 (66.7%)	1 (33.3%)	1.000
Pediatric Surgeon	1 (0.5%)	0 (0%)	1 (100%)	0.380
Scores				
BPRS	19.3±5.0	19.61±4.9	18.75±5.2	0.253
PWBS	41.2±8.2	40.99±8.6	41.45±7.6	0.711
SWLS	21.8±6.7	21.26±6.8	22.58±6.4	0.191

Table 2. *Comparison of the scores of Brief Psychological Resilience Scale, Psychological Well-Being Scale and Satisfaction With Life Scale according to the branches of resident physicians*

	Branches	n	Mean	Standard deviation	F	p
BPRS	Emergency Medicine	26	18.12	4.685	0.819	0.4
	Internal Medical Science	107	19.48	5.182		
	Surgical Medical Science	54	19.46	4.824		
PWBS	Emergency Medicine	26	40.27	6.685	7.029	0.001
	Internal Medical Science	107	42.95	7.846		
	Surgical Medical Science	54	38.06	8.625		
SWLS	Emergency medicine	26	19.19	6.132	9.745	0.001
	Internal Medical Science	107	23.54	6.156		
	Surgical Medical Science	54	19.46	6.949		

BPRS: Brief Psychological Resilience Scale; PWBS: Psychological Well-Being Scale, SWLS: Satisfaction with Life Scale.
Statistical analysis: One Way Anova test.

As a result of the study, the psychological resilience scores of resident physicians did not differ statistically (p=0.442) compared to the branch groups (emergency, internal, surgical); However, the scores of psychological well-being (p=0.001) and life satisfaction scores (p=0.001) showed statistically significant difference based on the branches (emergency, internal and surgical) (Table 2).

It was found that there was no statistically significant difference between the emergency and the internal and surgical medical science in terms of the psychological well-being of the residents (p=0.371, p=0.732); However, there was a significant difference between the internal and surgical medical science on behalf of the physicians working in the internal medical science (p=0.001) (Table 3).

The study determined that the highest life satisfaction belonged to the resident physicians working in internal medical science (Table 2). When the analysis conducted to determine the source of the difference between the life satisfaction of the resident physicians participating in the study was analyzed, there was a statistically significant difference between the life satisfaction of the resident physicians working in the emergency department and internal medical science (p=0.006); no statistically significant difference was found between the emergency medicine and the surgical medical science (p=1.000) (Table 3).

Discussion

In the literature, there was generally no difference between genders in terms of well-being and psychological resilience[10–13]. However, some studies have shown that women are well-being with scales that are more extreme[10], and it is stated that they are more exposed to stress and depressive symptoms. In addition, it is thought that it may be a common situation for women think that living conditions do not meet these expectations even though they may want more equality to regulate their lives in the early stages, lowering their life satisfaction levels. The role conflicts between working women on work-family

Table 3. *Evaluation of the analysis to determine the source of difference regarding Psychological Well-Being Scale and Satisfaction With Life Scale scores according to the branch groups of resident physicians*

	Branches	Comparison Group	p
PWBS	Emergency Medicine	Internal Medical Science	0.371
		Surgical Medical Science	0.732
	Internal Medical Science	Emergency Medicine	0.371
		Surgical Medical Science	0.001
	Surgical Medical Science	Emergency medicine	0.732
		Internal Medical Science	0.001
SWLS	Emergency Medicine	Internal Medical Science	0.006
		Surgical Medical Science	1.000
	Internal Medical Science	Emergency Medicine	0.006
		Surgical Medical Science	1.000
	Surgical Medical Science	Emergency Medicine	1.000
		Internal Medical Science	0.001

PWBS: Psychological Well-Being Scale, SWLS: Satisfaction with Life Scale.
Statistical analysis: Bonferroni test as Post Hoc test.

balance may also affect their well-being. Despite all these unfavorable causes, there should be reasons why women do not differ in their averages from men. It can be considered an advantage for men to be more independent and free in social life, to benefit more from the methods of coping with stress and to externalize their problems. Emotional intelligence averages of women who are known to have higher average effects their relationship with other people can increase their empathy and self-expression, thereby indirectly increasing their well-being and life satisfaction. Part-time working conditions can facilitate the preservation of work-family balance, reduce the perception of role conflict, and increase well-being. Role conflict and work-family balance influence well-being, and part-time compared to full-time work is associated with higher life satisfaction among career women[14]. Our study determined that the psychological resilience scores, stress coping, psychological well-being scores, and life satisfaction scores of resident physicians did not differ significantly according to their gender. Because resident physicians cannot work part-time, they are constantly working on shifts and this can not allocate enough time for their families, themselves, and social and private life. This situation does not distinguish gender for resident physicians. The fact that assistant physicians participating in our study are in the same city, in the same hospital, and under similar responsibilities can be considered a limitation of our study.

Another reason that determines the severity of stressors on resident physicians may be the branch they work for. Even though the resident physicians in the study work within the same institution, the departments they work for have different dynamics and stress factors. Studies in the literature report that surgeons are faced with more stress and workload and are more inclined to quit the training program[15–18]. The emergency department is the clinic with the highest patient density for many reasons, which significantly increases the workload. Health policies in our country, the fact that the patient has to pay a wage difference in other polyclinics and no wage difference in the emergency department, and other public and private employees' being transferred to the emergency department by administrators due to problems in getting consent for being off work and getting a health report instead, the fact that patients think they can more quickly resolve their problems in the emergency department and being in the emergency department grants them a priority for the resolution of their problems even though emergency department exists for urgent cases increase the workload of the emergency department. These reasons result in a severe increase in the density and, consequently workloads of the emergency departments in the Training and Research Hospitals, which are applied more intensively by patients than in university hospitals. It is also likely that residents working in Emergency Medicine Clinics in Training and Research Hospitals will undergo adverse effects regarding their stress, well-being, and life satisfaction levels due to the facts above. Although emergency medicine is among the internal medical science in our country during the specialty training process, it is closer to surgical medical science in terms of the interactions between stress, well-being, and life satisfaction.

A high level of psychological resilience is closely correlated with the ability to cope with stress. It was found that the participant's level of coping with stress based on their psychological resilience was not statistically different when compared among the branch groups (emergency, internal, surgical). Even though stress factors and workloads on resident physicians are high, the reason why there is no difference between the branch groups can be the fact that physicians improve themselves regarding psychological resilience; they are aware of the difficulties of the chosen branch as they deliberately have chosen it, they gain flexibility or and they accept the difficulties in some way even if they cannot get adapted to them.

When the results of the Psychological Well-Being Scale used in our study were examined, resident physicians working in internal medical science had higher psychological well-being than the physicians working in emergency medicine and surgical medical science, which can be explained by the fact that they can find more rest periods during working hours. There are relatively fewer stress factors they are exposed to during active work. In addition, they have relatively less workload, more hope for the future, and more time for themselves and their development families. It is not surprising that physicians in surgical medical science have the lowest psychological well-being due to their low scores, which stem from the opposite of reasons listed for internal medical science physicians.

One of the most basic elements necessary for one's life to make sense and leading a happy life is life satisfaction. This study determined that the highest

life satisfaction belonged to the resident physicians working in internal medical science. Life satisfaction comprises six elements: income level, occupational and social position, welfare level, state policy, opportunities and their conditions, environment, family, and social relations[19]. Residents cannot see the praise and appreciation they expect due to their professional and social positions. They think they can get the work done neither financially nor spiritually despite their heavy workload and responsibilities. It is thought that the current state policies are not implemented in favor of them sufficiently. The conditions they are in are not intended to decrease stress but rather to increase it. They are worried about their future, lack time for their private, family, and social lives, and their welfare levels do not meet their expectations. Our study has stated many times that these conditions are more evident, especially for resident physicians working in surgical medical science and emergency medicine. Even though emergency medicine is located in internal medical science in Education and Research Hospitals, the number of patients and their relatives, heavy workload, intense working hours, the fact that the possibility of rest during working hours is limited and sometimes nonexistent at certain hours, the residents here cannot spare enough time for their social lives, families, and development make us see the reason why emergency residents' life satisfaction scores are closer to surgical medical science. If we consider life satisfaction as a positive perception of the entire life of each individual, this is a result expected by us.

There is an intimate interaction between well-being and psychological resilience. Well-being makes it easier to cope with stress, and people with a high ability to cope with stress have higher well-being levels. On the contrary, excessive stress and low well-being levels can also impair people's health in all respects[20,21], negatively affect functionality and efficiency[22], and increase physician errors, risk of work accidents, and they're being burnout and exhausted[23]. For this reason, re-arranging the working hours considering the well-being of resident physicians in a way their ability to cope with stress is minimally affected and arranging the resident physicians' wages considering the difficulty of their work, the level of education required, the working hours, all the risks they take and personal depreciation during work may help to minimize stress. Furthermore, considering their expectations in terms of effective performance evaluation and effective use of different fields in specialty training such as rotation programs can contribute to the physician's motivation. In addition, equal distribution of workloads in clinics by administrators and physicians who are responsible for clinics according to the knowledge, skills, and seniority of resident physicians, a balanced implementation of the promotion and reward system, and making a fair arrangement can also enhance the efficiency and well-being of physicians. Keeping the well-being of the physicians high with the precautions to be taken will positively impact both their health and the patients they provide healthcare services to, as this will allow the physicians to be aware of their own capacities and ability to cope with stress. Besides, their psychological resilience, functionality, and efficiency will increase during this while.

Study Limitations

Our study was conducted in a single education and research hospital may create a limitation. Therefore, generalizing all resident physicians in our country may cause misconceptions. It may be useful if the prospective studies are conducted in a wider universe. The reliability and validity of the scales we used in our study have been studied and demonstrated, which one of the strengths of our study's strengths.

Conclusion

The decrease in physicians' well-being and psychological resilience should be perceived as an important public health problem. The factors that adversely affect the well-being of physicians and cause an increase in their stress levels are very diverse. Institution managers need to fulfill their responsibilities in creating an efficient working environment that enhances the well-being of physicians. Moreover, the staff's trust should be gained, and they should be supported. Positive interventions in the health system include parameters to reduce stressors on physicians, which will increase the efficiency and functionality of physicians and contribute to higher levels of health care.

Ethics Committee Approval

This study started after obtaining ethics approval from the T. C. Cukurova University Medical Faculty, Hospital Scientific Research Evaluation Commission (Date of Approval: 08.03.2019 Decision Number: 17 Number: SBÜANEAH. EK. 2019/86).

Authorship Contributions

Concept: T.E., S.A., S.S., Design: T.E., S.S., F.C.O., Data Collection or Processing: T.E., S.A., M.G., A.D., Analysis or Interpretation: T.E., S.A., S.S., C.I., A.D., M.G. Literature Search: T.E., S.A., S.S., F.C.O., C.I. Writing: T.E., S.A., S.S., M.G.

Conflict of Interest

The authors declared no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Donor Field Morbidity After Mosaicplasty Application in the Healthy Knee Joint

Sağlıklı Diz Ekleminde Mozaikplasti Uygulaması Sonrası Gelişen Donör Saha Morbiditesinin Değerlendirilmesi

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ABSTRACT

Aim: *This study investigates the donor site morbidity that develops in patients who received autologous osteochondral grafts from the ipsilateral healthy knee with the Mosaicplasty technique due to talus chondral lesion to investigate its relationship with age, gender, body mass index, number of grafts and diameter.*

Material and Method: *20 patients with talus chondral lesion underwent osteochondral transfer from the same-sided healthy knees using the Mosaicplasty technique. The mean age of the patients at surgery was 36.15; the mean follow-up time was 25.99 months; the mean body mass index was 26.51. The mean graft diameter was 0.87 cm, and the mean number of grafts was 1.5. Lysholm and VAS scores were evaluated. Kellgren-Lawrance classification was used for radiological changes.*

Results: *Donor site morbidity was observed in 4 patients. Two patients had mild knee pain, and one had moderate knee pain. It was observed that the number of grafts taken, age, and body mass index negatively affected Lysholm scores in the final follow-ups after the surgery, and VAS scores were lower in females.*

Conclusion: *In this study, no symptoms were observed in 80% of patients who harvested osteochondral grafts from their healthy knees. However, it is necessary to keep in mind the potential morbidity that may develop in the healthy knee joint after osteochondral transfer to the talus cartilage lesions, especially due to the low Lysholm scores detected in patients over 40 years of age with a body mass index ≥25 and who harvested more than one graft.*

Key words: *articular cartilage lesions; donor-site morbidity; mosaicplasty; osteochondral; knee*

ÖZET

Amaç: *Talus kondral lezyonu nedeni ile aynı taraf sağlıklı dizlerinden Mozaikplasti tekniği ile otolog osteokondral greft alınan hastalarda gelişen donör saha morbiditesinin incelenmesi ve bunun yaş, cinsiyet, vücut kitle indeksi, alınan greft sayısı ve çapı ile olan ilişkisinin araştırılmasıdır.*

Materyal ve Metot: *Talus kondral lezyonu olan toplam 20 hastaya aynı taraf sağlıklı dizlerinden Mozaikplasti tekniği kullanılarak osteokondral transfer işlemi uygulandı. Hastaların cerrahi sırasında ortalama yaşları 36,15, ortalama takip süresi 25,99 ay, ortalama vücut kitle indeksi 26,51 idi. Ortalama greft çapı 1,07 cm, ortalama greft sayısı 1,5 olarak saptandı. Lysholm ve VAS skorları değerlendirildi. Olası osteoartritik değişiklikler için Kellgren-Lawrance sınıflaması kullanıldı.*

Bulgular: *Toplam 4 hastada donör saha morbiditesi gözlendi. İki hastada hafif, bir hastada ise orta derecede diz ağrısı mevcuttu. Hastaların ameliyat sonrası yapılan son kontrollerinde alınan greft sayısı, yaş, vücut kitle indeksindeki artışın Lysholm skorlarını negatif yönde etkilediği, VAS skorlarının ise kadın cinsiyette daha düşük olduğu gözlendi.*

Sonuç: *Bu çalışmada sağlıklı dizlerinden osteokondral greft alınan hastaların %80'inde herhangi bir yakınma gözlenmedi. Ancak özellikle 40 yaş üstü, vücut kitle indeksi ≥25 olan ve birden fazla greft alınan hastalarda saptanan düşük Lysholm skorları nedeniyle talus kıkırdak lezyonlarına osteokondral transfer işlemi sonrası sağlıklı diz ekleminde gelişebilecek potansiyel morbiditenin akılda tutulması gereklidir.*

Anahtar kelimeler: *eklem kıkırdak lezyonları; donör saha morbiditesi; mozaikplasti; osteokondral; diz*

Introduction

Due to the limited spontaneous healing capacity of the avascular and hypocellular structure of the articular cartilage, the surgical treatment of full-thickness cartilage lesions, especially in load-bearing joints, is a clinical problem[1,2]. Arthroscopic debridement of the cartilage lesion, bone marrow stimulation, autologous osteochondral transfer (OOT), and autologous chondrocyte implantation is among the surgical treatments defined in cartilage lesions[1–5]. Although arthroscopic debridement and bone marrow stimulation provide

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satisfactory results in the short term, it has been reported that patient satisfaction decreases in the long term[3–5]. In the surgical treatment of full-thickness cartilage lesions, the OOT procedure with the Mosaicplasty technique transfers cylindrical grafts containing living cartilage tissue from the intact cartilage area subchondral bone tissue under it to the damaged cartilage area[2,5–7]. In this technique, the knee joint is the most preferred joint for the donor site, and the medial and lateral trochlear non-load-bearing parts of the femoral condyle are ideal areas for graft harvesting[2,5,8]. After the graft is taken, healing is observed in the donor site with cancellous bone underneath and fibrocartilage-like tissue on the joint surface[8,9]. Although it is seen as an important advantage of the Mosaicplasty technique as it allows living cartilage tissue to be transported to the damaged area with a single-stage surgical procedure, complaints such as pain, patellofemoral problems, effusion, crepitation, instability, i.e., donor site morbidity (DSM) in the donor site is a majordisadvantage[2,6,10].

In this study, we aim to examine DSM that developed in patients who received autologous osteochondral grafts with the Mosaicplasty technique from ipsilateral healthy knees due to talus chondral lesion and to investigate the relationship of this morbidity with age, gender, body mass index (BMI), number of grafts and diameter.

We hypothesize that DSM will increase as the number of grafts taken from the donor site or an increase in graft size; an increase in BMI and age negatively affect clinical outcome scores, and gender will not affect DSM.

Material and Method

After the local ethics committee decision with the number 28.06.2021–114/11 and the name of 'retrospective analysis of donor site morbidity after mosaicplasty application in the healthy knee joint,' we retrospectively studied a series of 24 patients who harvested osteochondral autografts from their ipsilateral intact knees for the surgical treatment of symptomatic talus osteochondral lesion between January 2016 and November 2020. Thirteen of the patients were male, and 11 were female. Inclusion criteria of patients in the study:

1. Patients with a follow-up period of at least six months,
2. Patients who have not had previous surgery on the knee to which osteochondral transfer was performed and who do not have any knee complaints,
3. Patients with regular follow-up, sufficient data, and knee radiographs of sufficient quality.

A total of 4 patients were excluded from the study, two of whom did not come for regular follow-up and two whose radiographs were not of sufficient quality. Thus, 20 patients, ten men and ten women were included in the study. The mean age of the patients at the time of surgery was 36.15 (19–54), and the mean follow-up period was 25.99 months (6 months-64 months). The mean BMI of the patients was 26.51 (22.21–37.46). Graftharvestingwas performed from the right knee in eight patients and from the left knee in twelve patients (Table 1).

Arthrex (Arthrex, Naples, FL) press-fit OOT system was used for graft harvesting from the donor site in all patients. This system allows 6, 8, 10 and 12 mm osteochondral cylindrical grafts to be taken from the donor site. For osteochondral graft harvesting, lateral parapatellar arthrotomy was used in all patients, and areas adjacent to the trochlear part of the ipsilateral lateral femoral condyle were preferred (Fig. 1). One autologous graft was harvested in 10 patients and two autologous grafts in 10 patients. In all patients, the recipient area was the talus superomedial articular surface in the ipsilateral ankle joint. Chevron-type osteotomy was applied to the medial malleolus in all patients to reach the medial cartilage lesion to the talus. The recipient area, where the cartilage defect on the talus joint surface is located, was prepared with the help of a cannulated reamer by the diameter and length of the osteochondral graft taken from the femur, and the graft taken from the donor area was impacted on the recipient area. Two 4.0 mm cannulated screws were used to fix the medial malleolus. The defect formed in the donor site was filled with subchondral bone obtained from the recipient site (Fig. 2). A 24-hour hemovac drain was used for the knee joint in all patients postoperatively. Movement exercises were started after the drains were removed. Complete weight-bearing restriction was applied to the patients for the first six weeks after surgery. In the following period, they were allowed to weigh as much as they could tolerate. No postoperative infection was observed in any patient. One patient observed hemarthrosis in the knee joint on the 2nd postoperative day. This patient was treated by aspiration and cryotherapy. In the postoperative 1-month follow-up of the patient, it was noted that the swelling in the knee joint was minimized. All patients had a minimum 6-month follow-up.

Knee flexion-extension intervals were detected in the clinical examinations for the knee joints at the final

Table 1. *Patient demographics*

	Minimum	Maximum	Average	Std. deviation
Age	19	54	36.15	±11.69
Weight (kg)	58	110	78.90	±11.98
Length (cm)	155	191	172.65	±11.34
BMI	22.21	37.46	26.51	±3.83
Follow up period (mo)	6	64	25.99	±12.17

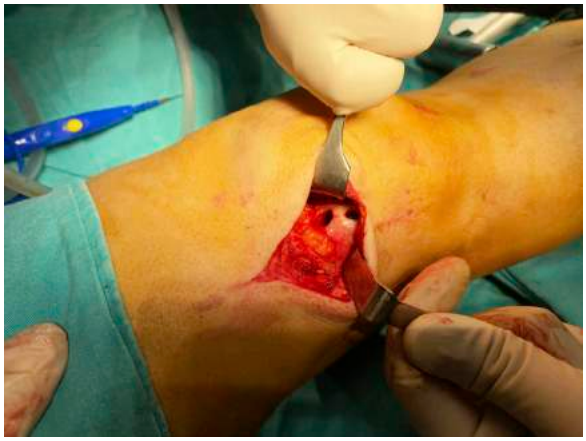

Figure 1. *Donor field image after graft removal.*

Figure 2. *Donor site image before surgical site closure.*

controls. Lysholm and VAS (Visual Analog Scale) scores were evaluated. In the radiological examination, possible osteoarthritic changes were recorded on the knee's anteroposterior, lateral and tangential patella radiographs.

Data were recorded on the computer, and Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL, USA) was used for biostatistical analysis. The Mann-Whitney U test compared means. The level of significance was set at $p<0.05$.

Results

Lysholm score was accepted as 100, and VAS score for knee joints was accepted as 0 since no patient had any problems and complaints in the preoperative knee clinical examinations. The mean postoperative Lysholm score of the patients was recorded as 83.25 (29–100). The mean postoperative VAS score of the patients was 2.55. When Lysholm scores were evaluated, excellent results were obtained in 10 patients (95–100), good results in 4 patients (84–94), intermediate results (83–65) in 3 patients, and poor results (<65) in 3 patients. The mean American Foot and Ankle Score was 51.05 (29–68) before the operation, while 89.35 (72–100) postoperatively.

When the knee flexion and extension ranges of the patients were evaluated, no limitation was observed in any of the patients. In the examination of knee complaints at the final follow-ups after the surgery, two patients had knee pain, one had knee joint effusion, and one had a locking sensation. Three of these patients were female, and one was male. The first of the patients with knee pain started by walking about 500 m, and the other patient had pain especially by pressing on the lateral condylar region of the femur. On the other hand, the patient who complained of locking sensation had problems, especially during stair climbing and squatting movements.

Patients were divided into two groups with BMI below 25 and above. There were nine patients with BMI <25 in the first group and 11 patients with a BMI ≥25 in the second group. When the VAS scores for knee pain were evaluated, the mean postoperative VAS score was 1.11 (0–2) in the first group and 3.73 (0–7) in the second group. The difference was not statistically significant. ($p=0.529$) While the mean postoperative Lysholm score was 94.0 (79–100) in the patients in the first group, this value was 74.45 (29–100) in the second group. The difference was statistically significant ($p=0.031$) (Table 2).

Patients were divided into two groups according to the number of grafts harvested from the lateral condyle of the femur. Ten patients with one graft number were in the first group, and ten patients with two grafts were in the second group. The mean postoperative Lysholm score was 91 (43–100) in the first group and 73.20 (29–83) in the second group. The difference was statistically significant. ($p=0.035$) While the mean postoperative VAS score was 1.40 (0–3) in the first group, it was 3.70 (0–7) in the second group. The difference was statistically insignificant ($p=0.089$) (Table 3).

Patients were divided into two groups according to the diameter of the graft harvested from the donor site. Ten patients with a graft diameter of less than 1 cm were in the first group, and ten patients with a graft diameter of 1 cm or more were in the second group. The mean postoperative Lysholm score was 77.30 (29–100) in the first group and 89.20 (71–100) in the second group. The difference was not statistically significant. ($p=0.481$) While the mean postoperative VAS score was 2.90 (0–7) in the first group, it was 2.20 (0–6) in the second group. The difference was statistically insignificant ($p=0.684$) (Table 4).

When the relationship between age with VAS and Lysholm scores was evaluated, the mean VAS score after surgery was found to be 1.80 (0–6) in patients younger

than 40 years of age (n: 10) and 3.30 in patients over 40 years of age (n: 10). It was observed that the difference was not statistically significant. (p=0.105) Lysholm score was 94.70 (77–100) preoperatively and 71.80 (29–96) postoperatively. The difference was statistically significant. (p=0.004) (Table 5).

Next, the relationship between gender and postoperative VAS and Lysholm scores was examined. The mean postoperative VAS score was 3.70 (1–7) in female patients, while it was 1.40 (0–3) in male patients. The difference was statistically significant. (p=0.019). Lysholm score was 73.40 (29–100) in women and 93.10 (71–100) in men after surgery. The difference was statistically significant (p=0.043) (Table 6).

The patients were not evaluated for knee osteoarthritis preoperatively but did not complain of knee pain. When the anteroposterior and lateral knee radiographs and tangential patella radiographs taken at the last follow-up of the patients were evaluated according to the Kellgren-Lawrance classification, it was found that 17 patients had stage 0, 2 patients had stage 1 (asymptomatic), and one patient had stage 2 osteoarthritis. A male patient with Kellgren-Lawrance Stage 2 osteoarthritis had a 56-month follow-up period, and osteophytes were located on the lateral patella.

Discussion

The most important finding of this study was that increasing the number of autologous grafts taken from the femoral area and increasing values of age and BMI negatively affected the Lysholm knee score. In addition, it was observed that the number of grafts taken after the surgery, diameter, BMI, and age increase did not affect the VAS score negatively. Still, the female gender negatively affected the VAS score.

A limited number of publications in the literature investigating DSM development after graft removal from a healthy knee. Nakagawa et al. reported that 85% of patients who harvestedosteochondral grafts from a healthy knee are asymptomatic[8]. Matsuura et al.[11] emphasized that the DSM rate increased to 2.3% when the general criteria were applied, but it increased to 12.8% when the sharper criteria were used; in the mosaicplasty procedure, they applied from the healthy knee in juvenile athletes with capital osteochondritis dissecans. Paul et al.[12] reported that five of 112 patients were moderately dissatisfied with their knees and six were severely dissatisfied with their knees in a large-series cohort study in which they had osteochondral lesions of the talus and applied mosaicplasty and followed up for more than two years. Nishimura et al.[13] found weakness in the knee extensor strength compared to the other knee in 8 of 11 patients they transferred from the intact opposite knee

Table 2. *VAS and Lysholm scores according to body mass index*

BMI		VAS	Lysholm
BMI <25	Average	1.11	94
	Std. deviation	±0.601	±6.856
	Minimum	0	79
	Maximum	2	100
BMI ≥25	Average	3.73	74.45
	Std. deviation	±2.102	±23.058
	Minimum	0	29
	Maximum	7	100
	p	0.529	0.031

Table 3. *VAS and Lyshholm scores by number of grafts*

Number of plugs		VAS	Lysholm
1	Average	1.40	93.30
	Std. deviation	±0.843	±8.908
	Minimum	0	70
	Maximum	3	100
2	Average	3.7	73.20
	Std. deviation	±2.312	±23.213
	Minimum	0	29
	Maximum	7	100
	p	0.089	0.035

Table 4. *VAS and Lyshholm scores according to graft diameter*

Graft Diameter		VAS	Lysholm
Diameter of plugs <1 cm	Average	2.90	77.30
	Std. deviation	±2.424	±25.613
	Minimum	0	29
	Maximum	7	100
Diameter of plugs ≥1 cm	Average	2.20	89.20
	Std. deviation	±1.687	±10.390
	Minimum	0	71
	Maximum	6	100
	p	0.684	0.481

Table 5. *VAS and Lyshholm scores by age*

Age		VAS	Lysholm
Age <40	Average	1.80	94.70
	Std. deviation	±1.751	±7.528
	Minimum	0	77
	Maximum	6	100
Age ≥40	Average	3.30	71.80
	Std. deviation	±2.163	±22.240
	Minimum	1	29
	Maximum	7	96
	p	0.105	0.004

Table 6. *VAS and Lyshholm scores by gender*

Gender		VAS	Lysholm
Female	Average	3.70	73.40
	Std. deviation	±2.214	±23.396
	Minimum	1	29
	Maximum	7	100
Male	Average	1.40	93.10
	Std. deviation	±1.075	±8.925
	Minimum	0	71
	Maximum	3	100
	p	0.019	0.043

for the osteochondral lesion in the humerus capitellum. Still, they stated that all patients reached preoperative knee strength within the first year after the surgery.

Pain, effusion, patellofemoral problems, limitation of movement, crepitation, and locking sensation are among the most important causes of DSM in the knee joint after osteochondral graft harvesting[2,8,10,11,13–15]. Andrade et al.[2] stated that the most common DSM observed in mosaicplasty applied from the knee to the ankle is pain and instability observed during daily or sports activities. Bexkens et al.[14] found the most common pain (7.8%) and locking sensation (0.8%) during daily activities in patients who applied osteochondral transfer to the humerus capitellum from the healthy knee. Valderrabano et al.[15] reported knee pain in 6 (50%) of 12 patients who underwent mosaicplasty for an osteochondral lesion of the talus in the knee joint. The current study observed DSM in 4 patients (20%).

Two grafts were harvested from the lateral condyle of the femur in one of the two patients with knee pain. In the other patient, the graft diameter was 1 cm. The first of the patients with knee pain started by walking about 500 m, and the other patient had pain especially by pressing on the lateral condylar region of the femur. The patient who developed hemarthrosis in the knee also had two grafts of 1 cm from the knee. It was observed that the postoperative swelling of the patient, for whom aspiration, cryotherapy, and elevation were applied, was minimized and did not affect the knee functions. The other patient complained of a locking sensation and described stuttering in the knee, especially during stair climbing and squatting movements. This patient underwent diagnostic arthroscopy at six months postoperatively. During the arthroscopic procedure, it was observed that the fibrocartilage-like tissue grew excessively in the grafted area. Following the shaving of the overgrown tissue, it was observed that the complaints of locking sensation were resolved at the last control of the patient.

When the relationship between DSM and age was investigated: Woelfle et al.[16] found a significant decrease in Hospital for Special SurgeryPatella scores in patients over 40. Al-Skaikh et al.[17] also reported that Lysholm scores in patients under 30 years of age were significantly better than those over 30. In contrast, Reddy et al. said that they did not detect a relationship between DSM with age[18]. The current study determined that Lysholm scores in patients under 40 years of age were significantly better than those over 40 years of age. Seven female and three male patients in the study group were over 40 years old. The VAS scores were worse in the patients over 40, but the difference was not statistically significant.

Regarding the relationship between DSM and age, Paul et al. indicate that the increase in BMI negatively affects Lysholm and WOMAC scores in patients undergoing osteochondral transfer to the ankle and that Lysholm score is more sensitive in terms of showing symptoms that occur in the early postoperative period, as it focuses on knee functions[12]. Matsuura et al.[11] argue that the patient populations are very young and have a low BMI, which may have led to DSM at a low rate of 2.3%. Similarly, Kim et al. report that patients with a BMI lower than 26 have a lower DSM and a higher Tegner activity score[19]. However, Woelfle et al. interpret that the VAS score is lower and the AOFAS score is higher in patients with a BMI above 25, probably due to the lower expectation of physical activity in this patient group[16]. In the current study, while the Lysholm score was 74.45 in patients with BMI ≥25, this value was 94 in patients with a BMI ≥25. This statistically significant value is important in terms of showing that postoperative knee functions can be negatively affected in overweight patients. We think the different pain thresholds can explain the statistically insignificant post-operative mean VAS values in both groups in each patient and the subjective nature of VAS values.

Studies published with different results regarding the relationship between diameter and number of tubular grafts harvested from the femoral condyle and DSM. Reddy et al. did not find a relationship between the number and diameter of grafts taken and DSM[18]. The same result was reported by Andrade et al.[2] and Paul et al.[12] Al-Shaikh et al.[17] said knee scores were worse in patients who received two grafts than those who received one graft. In their experimental studies on cadaver knees, Guetller et al.[20] showed that donor site defects up to 5 mm created in the periphery of the lateral femoral condyle in the upper part of the sulcus terminalis were not affected by patellar contact pressure. They also believe that additional lateral release may be meaningful in reducing the pressure this region is exposed to, so that lateral release may be preferred in larger donor site defects. In the current study, a single graft was taken in 10 patients, and two grafts were taken in 10 patients. It was observed that Lysholm scores were lower in patients with large graft diameters, but VAS scores were not affected by the number of grafts taken and the diameter of the graft.

When the effect of gender on DSM was examined, it was found that both Lysholm and VAS scores were lower in female patients. We think that the possible reason for this may be because there are seven female patients over the age of 40, and 6 (85%) of these patients have a BMI of ≥25.

This study includes some limitations. First, the study is retrospective. Second, the post-surgical donor site could not be evaluated with MR images or arthroscopically (except for one patient who underwent diagnostic arthroscopy after surgery). Third, our follow-up period is short to observe osteoarthritic changes that may develop in the donor site. The fourth is that the number of our patients is relatively small.

The study's strength is that it is the first study in our country to investigate the relationship of DSM with osteochondral graft diameter, number, BMI, age, and gender in OOT application from the ipsilateral healthy knee in talus chondral lesions.

Conclusion

In conclusion, in the surgical treatment of cartilage problems in load-bearing joints, OOT with the Mosaicplasty technique is a preferred method in that it can be applied with a single-stage surgery and allows the transfer of living cartilage tissue. In this study, the good and excellent results that we obtained in 17 patients in the transfer of osteochondral graft taken from the knee joint to the talus cartilage lesion for talus chondral lesions demonstrate the effectiveness of the OOT system. However, the Lysholm score decreases as the number of grafts taken from the knee joint, BMI, and age increases. Therefore the observation of DSM is among the undesirable effects of the system. Therefore, morbidity and osteoarthritic changes that may occur in the healthy knee joint after OOT for talus cartilage lesions should be kept in mind.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject nor from a company that provides or produces medical instruments and materials, which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, shareholding, and similar situations in any firm.

Authorship Contributions

Idea/Concept: H.A, O.Y.A; Design: B.K, M.A; Control/Audit: H.A.A, O.Y.A; Data Collection and/or Processing: O.Y.A, B.K; Analysis and/or Interpretation: M.A, H.A.A; Writing the Article: H.A, B.K; Critical Review: O.Y.A, H.A.A; Sources: H.A, M.A.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Healthcare Professionals and COVID-19 Vaccine: Approaches of Health Workers to Vaccination in the First Days of Vaccination

Sağlık Çalışanları ve COVID-19 Aşısı: Aşılamanın İlk Günlerinde Sağlık Çalışanlarının Aşıya Yaklaşımları

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ABSTRACT

Aim: *This study aims to determine healthcare professionals' knowledge, attitudes, and behaviors toward COVID-19 disease and vaccine in the first days of vaccination.*

Material and Method: *The study was conducted in Sakarya Yenikent State Hospital between March 1–15, 2021, where the 2nd vaccine should also be completed for healthcare workers. The ethics committee of the study was obtained from the ethics committee of Sakarya University Faculty of Medicine. Healthcare workers who agreed to participate in the study were asked to fill out the interview form. Data were analyzed in SPSS 21 program.*

Results: *Of the health workers participating in the study, 189 were female, and the median age was 37.0 [28.0–44.0]. The distribution of health workers by profession is examined; 115 nurses, 28 doctors, 35 technicians, 32 medical secretaries, 30 cleaning personnel, and 62 other occupational groups. During the last winter season, "Have you had the flu shot?" While 111 health workers answered "yes" to the question, 52 of those vaccinated reported that they had the flu vaccine this winter season as well. One hundred seventy-one healthcare professionals said they were involved in caring for COVID-19 patients. While there are 89 healthcare workers with COVID-19 infection, 34 healthcare professionals did not know whether they had COVID-19 infection. While only 87 participants reported that they had enough knowledge about COVID-19 vaccines, 113 stated that they had no information, and 102 were undecided on this issue. While 141 healthcare professionals are concerned about COVID-19 vaccines, 149 had concerns about vaccine protection. While 49 participants thought that inactivated vaccines were resistant to mutation and 28 thought that they were not resistant, 225 of them did not know about this issue. While 29 healthcare professionals think that mRNA vaccines produce more antibodies than inactivated vaccines, 26 health professionals stated that they disagreed with this, and 247 indicated that they did not know about this issue. While 129 health professionals did not know whether or not breastfeeding women should be vaccinated, 127 thought breastfeeding women should not be vaccinated, and 46 thought they should be vaccinated. While 245 healthcare professionals reported that they had the COVID-19 vaccine, 213 were recommended to their close friends, and 215 recommended the patients be vaccinated for COVID-19. The vaccines most trusted by healthcare professionals are Sinovac/Coronovac (47.7%), Biontech (18.5%), Domestic COVID-19 vaccine (5%), Oxford AZ (4.3%), Moderna (4%), and Sputnik V (3.3%).*

Conclusion: *In our study, it was concluded that in the first days of the application of the COVID-19 vaccine, healthcare professionals do not have enough knowledge about COVID-19 vaccines, they are worried about COVID-19 vaccines, and they are worried about the protection of the vaccine, and the most reliable COVID-19 vaccine is Sinovac/Coronovac vaccine. Multidimensional studies are needed to increase COVID-19 vaccination rates.*

Key words: *COVID-19 disease; COVID-19 vaccines; knowledge level; health workers*

ÖZET

Amaç: *Bu çalışmanın amacı, aşılamanın ilk günlerinde sağlık çalışanlarının COVID-19 hastalığı ve aşısına yönelik bilgi tutum ve davranışlarını belirlemektir.*

Materyal ve Metot: *Çalışma, sağlık çalışanları için 2. aşının da tamamlanmış olması gereken 1–15 Mart 2021 tarihleri arasında Sakarya Yenikent Devlet Hastanesi'nde yapıldı. Çalışmanın etik kurulu Sakarya Üniversitesi Tıp Fakültesi Etik Kurulu'ndan alındı. Araştırmaya katılmayı kabul eden sağlık çalışanlarından görüşme formunu doldurması istendi. Veriler SPSS 21 programında analiz edildi.*

Bulgular: *Sağlık çalışanlarının 189'u kadın ve yaş ortancası 37,0 [28,0–44,0] yıldı. Katılımcıların mesleklere göre dağılımları incelendiğinde; 115'i hemşire, 28'i doktor, 35'i teknisyen, 32'si tıbbi sekreter, 30'u temizlik personeli ve 62'si diğer meslek gruplarındandı. Sağlıkçıların 171'si COVID-19 hasta bakımında görev aldığını bildirdi. COVID-19 enfeksiyonu geçiren 89 sağlık çalışanı varken; 34'ü COVID-19 enfeksiyonu geçirip geçirmediğini bilmemekteydi. Katılımcıların yalnızca 87'si COVID-19 aşılarıyla ilgili yeterince bilgiye sahip olduğunu bildirirken; 113'ü bilgisi olmadığını ve 102'si ise bu konuyla ilgili kararsız olduğunu bildirdi. Sağlıkçıların 141'i COVID-19 aşıları hakkında kaygılanırken; 149'unun aşı koruyuculuğu hakkında endişeleri vardı. Katılımcıların 49'u inaktif aşıların mutasyona dayanıklı olduğunu, 28'i ise dayanıklı olmadığını düşünürken; 225'inin bu konu hakkında bilgisi yoktu. mRNA aşılarının inaktif aşılara göre daha çok antikor ürettiğini düşünen sağlık çalışanı 29 iken; sağlıkçıların 26'sı buna katılmadığını ve 247'si ise bu konu hakkında bilgisi olmadığını bildirdi. Emziren kadınların aşı olup olmaması hakkında sağlıkçıların 129'unun bilgisi yokken; 127'si emziren kadınların aşı olmaması gerektiğini ve 46'sı ise aşı olması gerektiğini düşünmekteydi. Sağlıkçıların 245'i COVID-19 aşısı olduğunu bildirirken; 213'ü yakın arkadaşlarına ve 215'i hastalara COVID-19 aşısı olmasını önermekteydi. Sağlık çalışanlarının en çok güvendikleri aşılar sırasıyla Sinovac/Coronovac (%47,7), Biontech (%18,5), Yerli COVID-19 aşısı (%5), Oxford AZ (%4,3), Moderna (%4) ve Sputnik V (%3,3) idi.*

Sonuç: *Çalışmamızda COVID-19 aşısının uygulandığı ilk günlerde sağlık çalışanlarının COVID-19 aşılarıyla ilgili yeterince bilgisinin olmadığı, COVID-19 aşılarıyla ilgili kaygılı ve aşının koruyuculuğuyla ilgili endişeli olduğu, en güvendikleri COVID-19 aşısının Sinovac/Coronovac olduğu sonuçlarına ulaşılmıştır. COVID-19 aşılama oranlarının arttırılması için çok yönlü çalışmalara ihtiyaç vardır.*

Anahtar kelimeler: *COVID-19 hastalığı; COVID-19 aşıları; bilgi düzeyi; sağlık çalışanları*

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Introduction

Uncertain and deadly pneumonia, which emerged in the Chinese city of Wuhan in late 2019, spread rapidly and affected the world. The World Health Organization (WHO) declared the disease caused by this new coronavirus as Coronavirus Disease-2019 (COVID-19). The International Committee on Taxonomy of Viruses (ICTV) named this new coronavirus SARS-CoV-2[1]. To date, COVID-19 disease has caused more than 213,205,948 infections and more than 4.452.460 deaths worldwide[2]. In COVID-19 patients, the clinic can range from mild clinical symptoms that do not require hospitalization to more severe symptoms that require hospitalization. In severe clinical patients, systemic multi-organ failure may develop, and serious life-threatening complications may occur, including acute respiratory distress syndrome (ARDS)[3].

SARS-CoV-2 can be transmitted rapidly through the respiratory tract, and thus the virus can spread easily[4]. Although it is important to apply standard precautions (mask-distance-cleaning) and restraint measures to control COVID-19 disease, these measures and precautions are insufficient to control the pandemic. Vaccination is the most effective method to prevent infections and reduce morbidity and mortality from infection[5]. With vaccination, life expectancy has increased significantly, society and the economy have begun to reshape fundamentally, and the devastating effects of many infectious diseases have diminished as vaccination becomes more widespread[6]. Although the treatment protocols with proven effectiveness in the treatment of COVID-19 are limited, vaccination and vaccine development studies continue. The aim of vaccine development and vaccine studies is to prevent the severity of the disease, the transmission of the viruses, and future infections[7]. The ongoing discussions about the COVID-19 pandemic and vaccines worldwide have caused hesitations against vaccines to increase. Concerns about the COVID 19 vaccine have been reported to occur due to the novelty and safety of the vaccine and its potential side effects. It is important to identify factors that cause uncertainty about vaccination against COVID 19. Because undecided individuals may be the most realistic targets for vaccination promotion and vaccination campaigns, understanding their concerns is crucial, as these individuals make up a larger proportion of the population than those who are confident they will not be vaccinated[8].

To protect against the COVID-19 epidemic, vaccination with a vaccine will undoubtedly be the best cost-effective way and will ensure the control of the disease. However, today, when there is confusion about vaccines, it is of great importance to use the right information sources to successfully combat the epidemic[9]. In addition to the media, healthcare professionals who set an example for society should inform and support people about vaccines accurately[10]. Thus, it is predicted that the vaccination rates in society will increase even more. This study aims to determine healthcare professionals' knowledge, attitudes, and behaviors about COVID-19 disease and vaccine in the first days of implementing the COVID-19 vaccine.

Material and Method

Study Design

This study is a descriptive cross-sectional study.

Place and Time of the Study

The study was carried out at Sakarya Yenikent State Hospital between 1–15 March 2021, when the 2nd vaccine should also be completed for healthcare workers.

Data Collection Tools

Demographic data and descriptive features form consists of 33 questions, including demographic data of healthcare workers, information about COVID-19 disease, and COVID-19 vaccines.

Ethical Approval of the Study

The ethics committee of the study was obtained from the ethics committee of Sakarya University Faculty of Medicine with the date 01.02.2021 and the number E-71522473-050.01.04-14836-116 and the research permission was obtained from the scientific research studies of the Ministry of Health in the same period.

Data Collection

After obtaining the necessary ethical and institutional permissions, healthcare professionals working at Sakarya Yenikent State Hospital who agreed to participate in the study were asked to fill out the interview form. The interview form consisted of "Demographical data and descriptive features Form" and "Information on COVID-19 vaccines". Before completing the interview form, consent was obtained from the health workers, and the researcher was informed that the information about the study would not be shared anywhere else and that the health workers could leave the study at any time. Filling in the interview form took an average of 5 minutes for each health worker.

Evaluation of Data

Data were analyzed using the IBM SPSS 22 (Armonk, NY: IBM Corp) statistical program11. Categorical

variables were shown as frequency and percentage values, and discrete variables were shown as the arithmetic mean standard deviation or median and interquartile range according to the results of the normal distribution test. The significance level was taken as $p<0.05$.

Results

Of the health workers participating in the study, 189 (62.6%) were female, and the median age was 37.0 [28.0–44.0]. 59 (19.5%) of the participants were high school graduates, 66 (21.9%) associate degree, 135 (44.7%) undergraduate and 42 (13.9%) graduate/doctorate graduates. When their distribution according to occupations is examined; 115 (38.1%) nurses, 28 (9.3%) doctors, 35 (11.6%) technicians, 32 (10.6%) medical secretaries, 30 (9.9%) cleaning staff and 62 (20.5) were from other occupational groups. Of the healthcare professionals, 72 (23.8%) were clinics, 65 (21.5%) were intensive care units, 32 (10.6%) were polyclinics, 24 (7.9%) were administrative units, and 18 (6.0%) were emergency services. 22 (7.3%) were working in the operating room, 16 (5.3%) were working in COVID-19 clinics, and 53 (17.5%) were working in other units. Of the participants, 56 (18.5%) had at least one chronic disease, and 63 (20.8%) had allergies. 67 (22.2%) were using drugs continuously; Seven of them (2.3%) were using immunosuppressive drugs. During the last winter season, "Have you had the flu shot?" While 111 (36.8%) health workers answered "yes" to the question, 52 (46.8%) of those who were vaccinated (n: 111) reported that they had the flu vaccine this winter season as well. While 171 (56.6%) of the healthcare professionals were involved in COVID-19 patient care, 89 (29.5%) healthcare workers stated that they had COVID-19 infection, and 34 (11.3%) healthcare workers did not know whether they had COVID-19 infection. While only 87 (28.8%) of the participants reported that they had enough information about COVID-19 vaccines, 113 (37.4%) stated that they had no knowledge and 102 (33.8%) stated that they were undecided on this issue. While 141 (46.7%) healthcare professionals were concerned about the COVID-19 vaccine, 149 (49.3%) stated that they were concerned about its protection. While 49 (16.2%) of the participants thought that inactivated vaccines were resistant to mutation, 28 (9.3%) thought that they were not resistant; 225 (74.5%) did not know this subject. While 29 (9.6%) healthcare workers thought that mRNA vaccines produced more antibodies than inactivated vaccines, 26 (8.6%) of the healthcare professionals did not agree with this, and 247 (81.8%) reported that they did not know about this issue. While 129 (42%) of the healthcare professionals were not informed about whether or not breastfeeding women should be vaccinated, 127 (42.1%) of the participants thought that breastfeeding women should not be vaccinated, and 46 (15.2%) thought that they should be vaccinated. The answers healthcare professionals give to questions about COVID-19 vaccines are shown in Table 1. While 245 (81.8%) of the healthcare professionals reported that they had the COVID-19 vaccine, 213 (70.5%) recommended it to their close friends, and 215 (71.2%) patients recommended the COVID-19 vaccine. Asked health workers, "Which COVID-19 vaccines do you trust?" Their answers to the question are presented in Fig. 1.

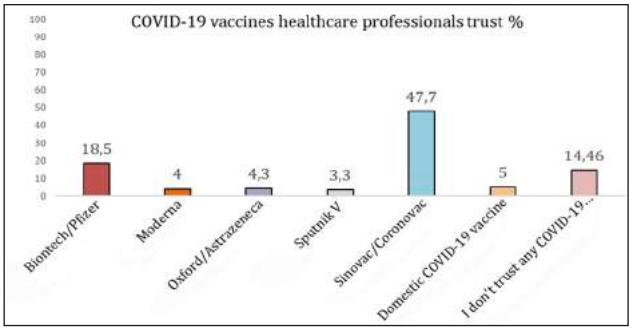

Figure 1. *COVID-19 vaccines healthcare professionals trust.*

Discussion

Vaccination is an effective, safe, and inexpensive method of preventing infectious diseases[12]. One of the most important components in controlling the COVID-19 pandemic is to provide the highest level of immunity with an effective and safe vaccine. In a study conducted in Iran[13], it was reported that 64.3% of the participants were willing to accept any COVID-19 vaccine. In contrast, in another study conducted in Kenya, 52.4% of Kenyans were ready to receive a COVID-19 vaccine[14]. In their study, Roy et al. reported that 63% of healthcare workers would be vaccinated against COVID-1915. In our study, the rate of healthcare workers vaccinated against COVID-19 in the first days of immunization was found to be 81.8%. It can be thought that this high rate of accepting the vaccine in the first days of immunization by healthcare professionals may be due to working in an environment where there is a risk of transmission and caring for a patient infected with COVID-19. In addition, it can be predicted that the cleaning-mask-distance rule alone is insufficient to prevent transmission and that the vaccine's acceptance rate is high due to the necessity of immunization

to prevent the disease. The results of our study were mostly compatible with the literature.

While information and sharing about the prevention of COVID-19 transmission and control measures continue, there is still uncertainty among individuals about the safety of vaccines. In a study, it was reported that health workers stated they were willing to be vaccinated against COVID-19, but 1 out of every six said they were reluctant to be vaccinated due to concerns about the lack of information about the efficacy and safety of the vaccine[15]. In a study conducted in Kenya, it was reported that the majority of those who did not want to be vaccinated were worried about the vaccine's side effects, so they did not want to be vaccinated. In our study, only 28.8% of healthcare professionals reported that their knowledge of COVID-19 vaccines was sufficient in the first days of the introduction of COVID-19 vaccines, 46.7% said that they were concerned about COVID-19 vaccines, and 49.3% reported that they had concerns about the protection of vaccines. . It was thought that healthcare workers were worried about constantly giving care to patients with COVID-19, being at risk for disease transmission, and the thought of infecting their families. To reverse the anxieties and concerns about the COVID-19 vaccine and to increase the level of trust and immunization rates, the ministry of health should organize programs through television programs and social media. Society should be informed about the importance of immunization in protection against COVID-19 infection, the protection rates of vaccines, and the side effects of vaccines.

The COVID-19 infection, which has surrounded the world and brought life to the point of paralysis, continues to negatively affect human life in many areas, especially in physical, social, economic, and psychological dimensions. Immunization with a vaccine will undoubtedly be the best cost-effective way to prevent the COVID-19 outbreak and ensure disease control. Development of vaccines and their implementation as soon as possible; As in other pandemics, it is important to prevent the spread of the disease in the community and serious effects such as severe illness and death in COVID-19 infection. However, in today's World, where there is a lot of confusion, anxiety, and concern about vaccines, it is

Table 1. *Responses of healthcare professionals to questions about COVID-19 vaccines*

Questions	N (%)
Those with COVID-19 infection should get the COVID-19 vaccine	213 (70.5)
Those with COVID-19 infection should have antibodies tested prior to the COVID-19 vaccine	176 (58.3)
Healthcare workers should be vaccinated against COVID-19	233 (77.2)
Individuals under the age of 18 should be vaccinated against COVID-19	77 (25.5)
Individuals with at least one chronic illness should have the COVID-19 vaccine	180 (59.6)
Individuals over the age of 50 should have the COVID-19 vaccine	180 (59.6)
Individuals over 50 years of age and with at least one chronic disease should be vaccinated against COVID-19	188 (62.3)
Individuals over the age of 65 should have the COVID-19 vaccine	199 (65.9)
Individuals over 65 years of age and with at least one chronic disease should be vaccinated against COVID-19	201 (66.6)
Individuals over the age of 80 should have the COVID-19 vaccine	179 (59.3)
Individuals over 80 years of age and with at least one chronic disease should be vaccinated against COVID-19	175 (57.9)
Individuals under the age of 18 should not be vaccinated	168 (55.6)
Those with drug allergies should not get the COVID-19 vaccine	134 (44.4)
Those with vaccine allergies should not get the COVID-19 vaccine	179 (59.3)
1st trimester pregnant women should not be vaccinated	203 (67.2)
2nd trimester pregnant women should not be vaccinated	142 (47.0)
3rd trimester pregnant women should not be vaccinated	138 (45.7)
Patients who had COVID-19 less than 3 months ago should not be vaccinated against COVID-19	59 (19.5)
Patients who had COVID-19 more than 4 months ago should not have the COVID-19 vaccine	31 (10.3)
It is inconvenient to have the influenza vaccine at the same time as the COVID-19 vaccine	45 (14.9)
Re-infection with COVID-19 can occur after contracting a COVID-19 infection	157 (52.0)
Can get COVID-19 infection after getting COVID-19 vaccine	217 (71.9)
After receiving the COVID-19 vaccine, 15-30 minutes should be waited in the institution	247 (81.8)
Get COVID-19 vaccine within 6 months of contracting a COVID-19 infection	148 (49.0)
COVID-19 vaccine does not completely prevent SARS CoV-2 transmission, but prevents severe COVID-19 disease	146 (48.3)

very important to use the right information sources to combat the epidemic successfully. At the end of the pandemic, countries should establish vaccination strategies that will cover all aspects of the society as soon as possible, maintain effective vaccination studies and ensure that the entire society is vaccinated[16].

As a result, In the first days of implementing the COVID-19 vaccine, it is clearly understood that the basic form of protection for healthcare workers is the three-way rule of the mask, distance, and cleanliness, as well as the acceptance of the COVID-19 vaccine. However, the constant risk of COVID-19 contamination brought by the pandemic seems to have caused anxiety, fear, and panic in healthcare workers. Accordingly, it appears to have significantly affected the view of COVID-19 vaccines.

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Conflicts of Interests

The authors report no conflicts of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Intensive Care Prediction During Treatment of Covid-19 Patients

Covid-19 Hastalarının Tedavisi Sırasında Yoğun Bakım Tahmini

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ABSTRACT

Aim: *We aimed to research the routine examinations, clinical and radiological findings of patients hospitalized with the diagnosis of Covid-19, the clinical course of the patients whose treatments were ongoing, and the markers that could predict the possibility of admission to the intensive care unit.*

Material and Method: *Retrospectively compared the examinations and findings on the day of hospitalization of the patients who were followed up for Covid-19 treatment with the data on the first day of their admission to the intensive care unit.*

Results: *Out of 195 patients treated with the diagnosis of Covid-19 in the service on the first day. Fever, shortness of breath, chest pain, and cough were the most common symptoms. Platelet and lymphocyte ratio was higher in the patients' first days in the service compared to the first days in intensive care, and the change that occurred was statistically significant (p<0.05). A significant difference was found between SOFA score and gender (p<0.05) and between SOFA score and age (p<0.05).*

Conclusion: *Covid-19 patients with comorbid diseases such as advanced age, diabetes, hypertension, heart and respiratory failure, and acute and chronic renal failure carry a higher risk.*

Key words: *intensive care; covid-19; PLR; SOFA score*

ÖZET

Amaç: *Covid-19 tanısıyla hastaneye yatışı yapılan hastaların rutin tetkikleri, klinik, radyolojik bulguları ile tedavisi devam eden hastaların klinik seyrini ve yoğun bakıma alınma ihtimalini önceden gösterebilecek belirteçleri araştırmayı amaçladık.*

Materyal ve Metot: *Covid-19 tedavisi için takip edilen hastaların hastaneye yatış günü muayene ve bulguları retrospektif olarak yoğun bakıma yatışlarının ilk günkü verileriyle karşılaştırıldı.*

Bulgular: *Serviste ilk gün Covid-19 tanısı ile tedavi edilen 195 hastadan. Ateş, nefes darlığı, göğüs ağrısı ve öksürük en sık görülen semptomlardı. Hastaların servisteki ilk günlerinde trombosit ve lenfosit oranı yoğun bakımdaki ilk günlere göre daha yüksek bulundu ve meydana gelen değişim istatistiksel olarak anlamlıydı (p<0,05). SOFA puanı ile cinsiyet arasında (p<0,05), SOFA puanı ile yaş arasında (p<0,05) anlamlı fark bulundu.*

Sonuç: *İleri yaş, diyabet, hipertansiyon, kalp ve solunum yetmezliği hastalıkları, akut ve kronik böbrek yetmezliği gibi komorbid hastalıkları olan Covid-19 hastaları daha yüksek risk taşımaktadır.*

Anahtar kelimeler: *yoğun bakım; covid-19; PLR; SOFA skoru*

Introduction

The Coronaviridae family, which includes different mammalian and animal pathogens, may cause different clinical pictures in humans, ranging from colds to severe respiratory diseases. Coronavirus infection emerged in Wuhan, China, in December 2019 and is called Covid-19 (2019-nCoV), following the Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV), which have been effective worldwide with the millennium and are epidemiologically considered zoonotic infections[1,2]. Coronaviruses can spread rapidly among infected cases and cause a worldwide pandemic[3]. In patients infected with Covid-19, it is difficult to isolate and diagnose the agent since different clinical pictures often occur, and some cases may be asymptomatic.

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Hence, it is important to perform a detailed physical, radiological, and laboratory examination[4,5]. The most common symptoms in Covid-19 patients were fever, cough, and fatigue. The definitive diagnosis is made with real-time Polymerase Chain Reaction (PCR), and the image of "ground glass opacity" in computed tomography helps the diagnosis[6,7,8]. Most patients with suspected Covid-19 are followed up on an outpatient basis since they do not have severe pneumonia findings. Some patients with negative PCR test results received anti-viral treatment due to ground glass appearance on thorax computed tomography (CT) [9]. While some patients admitted to the hospital are discharged after short-term treatment, some require intensive care due to severe respiratory distress and deterioration[10]. In suspicious cases admitted to the hospital, treatment of acute respiratory failure and hemodynamic support, isolation, and rapid diagnosis are needed. Decision-making processes can guide implementations in the follow-up[11]. This algorithm is important not only for the clinical follow-up and treatment plan of Covid-19 patients but also for healthcare workers and other patients at risk of nosocomial infection[12]. This study investigated the markers that could predict the possibility of the need for an intensive care unit in a tertiary hospital.

Materials and Methods

A retrospective analysis was conducted on admitted and confirmed Covid-19 cases at the Samsun Training and Research Hospital between March 11 – May 30, 2020. The same hospital conducted the study after the Ministry of Health Scientific Committee's approval with the form 2020-05-17T22_26_50, and the Local Ethics Committee dated 05.06.2020 and numbered Non-Interventional Clinical Research/2020/8/1.

Selection of Patients

For patients treated in the hospital with the diagnosis of Covid-19, the clinical picture worsened during their treatment, and patients who were taken into the intensive care unit were included in the study. The hospitalization period of the patients in the service was at least one day. While comparing the service and intensive care parameters of the patients, the parameters on the first day of the service admission were defined as the service period (SP) and the intensive care period (ICP) for the parameters on the first day in the intensive care unit.

Data Collection

Age, gender, hospitalization indication, indication for admission to intensive care unit, co-morbid diseases, CT evaluation, and PCR test result on the first day were obtained from patient records. The patients' routine biochemistry and complete blood count were evaluated according to the results of the first day of admission to the service and the first day of admission to the intensive care unit. The Sepsis-related Organ Failure Assessment (SOFA) was analyzed according to the day they were taken into intensive care.

Statistical Study

The data were analyzed using the statistical software SPSS 24 (Statistical Package for the Social Sciences–IBM®). Descriptive statistics were presented as numbers and percentages for categorical, mean ± standard deviation, or median for numerical variables. The normality of continuous variables was evaluated using the Kolmogorov-Smirnow test and the Shapiro-Wilk test. For comparison of numerical variables between groups, the Mann-Whitney U test was used for two independent groups; one Way Anova test or Kruskal-Wallis Method was used for more than two groups. Bonferroni Test was applied after multiple analyses. While the distribution relationship between categorical variables was analyzed with the Chi-Square test, the t-Test for Two Independent Groups was used to compare numerical data. The results were evaluated at a confidence interval of 95%, with a value of $p<0.05$ considered significant.

Results

Out of 195 patients that were included in our study, 105 (53.8%) were male, and 90 (46.2%) were female (Table 1). The average age of the patients was 69.77±15.73 years; the average age of women was significantly higher than the average age of men ($p<0.05$) (Table 1).

In SP of the patients, fever (n=x, 36.9%), shortness of breath (n=x, 80%), cough (n=x, 25.1%), and chest pain (n=x, 14.9%) were the most common symptoms. When the symptoms were analyzed in the ICP, 12.82% fever, 89.74% shortness of breath, 10.77% chest pain, and 15.9% cough were significant (Table 2).

In patients, 44.62% hypertension (HT), 14.36% Acute renal failure/Chronic renal failure (ARF/CRF), 23.59% heart failure, 15.38% Coronary Artery Disease (CAD), 18.97% Chronic Obstructive Pulmonary Disease

(COPD), 26.67% Diabetes Mellitus (DM), 12.31% cancer and 22.05% Cerebrovascular Disease (CVD) were the most common comorbid diseases (Table 3).

In the study, CT was performed in 95.38% of the patients who received treatment, 81.03% consistent with Covid-19, and 18.97% had non-infectious CT findings (Table 4). In ICP, 25.13% (n=49) patients required intubation (Table 2).

In the study, hemogram and biochemistry results in SP and ICP were compared in 2 groups; C-reactive Protein (CRP), white blood cell (WBC), erythrocyte (RBC), hemoglobin (Hb), hematocrit (Hct), platelet (Plt), absolute lymphocyte (Lym), monocyte, eosinophil, basophil, red blood cell volume (RDW), mean platelet volume (MPV), mean values of glucose, urea, and calcium were found to be lower than the results of the first day in service. However, absolute neutrophil (Neu), creatine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), retain kinase (CK), sodium, potassium, and chlorine values were observed to be higher than in the first day in the service. Increases and decreases in mean values of CRP, WBC, RBC, Plt, Lym, Neu, eosinophils, basophils, glucose, urea, AST, potassium, and chlorine were statistically significant ($p<0.05$) (Table 5).

The mean neutrophil/lymphocyte ratio (NLR) was 6.29±3.32 in SP and 8.56±3.26 in SP and ICP. No statistically significant difference was found in the NLR values of the groups ($p>0.05$). The mean platelet/lymphocyte ratio (PLR) was 241.7±58.99 in SP and 226.33±58.32 in ICP. The change in PLR values was found to be statistically significant ($p<0.05$) (Table 6).

In the study, the mean age of the patients with the SOFA score between 0–5 was 68.64±16.74 years, and the mean age of the patients with the SOFA score between 6–11 was 71.88±13.51 years. A statistically significant difference was found between SOFA score and age ($p<0.05$) (Table 7).

The PCR test we used for diagnosis was negative in 31.28%, positive in 59.49%, and not studied in 9.23% (Table 8).

Discussion

Covid-19 disease, which infects millions of people worldwide, affects older people with high comorbidities more and increases hospitalization rates. Due to the hospital's limited service and intensive care bed capacities, a good triage is required for patient admission to both services and intensive care units.

Table 1. *Demographic data*

		SG patients (n: 195)				t Test	P-value
		n	%	Avg ± Std	Min-max		
Age (years)	Female	90	46.2	72.63±15.05	24–92	**2.369**	**0.032***
	Male	105	53.8	67.32±15.95	20–92		
	Total	**195**	**100**	**69.77±15.73**	**20–92**		

Table 2. *Data on SG complaints, CUG patient complaints, and intubation status*

		SG patients (n: 195)		CUG patients (n: 195)		
	V/Y	n	%	n	%	p
Fever	Yes	72	36.92	25	12.82	**0.048***
	No	123	63.08	170	87.18	
Shortness of breath	Yes	156	80.00	175	89.74	**0.007***
	No	39	20.00	20	10.26	
Cough	Yes	49	25.13	31	15.9	**0.001***
	No	146	74.87	164	84.1	
Chest pain	Yes	29	14.87	21	10.77	**0.001***
	No	166	85.13	174	89.23	
Endotracheal intubation	Yes	-	-	49	25.13	
	No	-	-	146	74.87	

Table 3. *Presence of comorbid disease*

		SG patients (n: 195)	
Comorbid diseases	V/Y	n	%
HT	**Yes**	**87**	**44.62**
	No	108	55.38
ABY/KBY	**Yes**	**28**	**14.36**
	No	167	85.64
Heart failure	**Yes**	**46**	**23.59**
	No	149	76.41
CAH	**Yes**	**30**	**15.38**
	No	165	84.62
COPD	Yes	37	18.97
	No	158	81.03
DM	Yes	52	26.67
	No	143	73.33
Cancer	Yes	24	12.31
	No	171	87.69
CVD	Yes	43	22.05
	No	152	77.95

Table 4. *Data of the first day CT results in service*

		Patients who received treatment on the first day in the service (n: 195)	
		n	%
CT	Yes	186	95.38
	No	9	4.62
Compatible with COVID-19	Yes	158	81.03
Non-infectious finding	Yes	28	18.97

Table 5. *SG and CUG hemogram and biochemistry results*

	SG (n: 195)		CUG (n: 195)			
	Avg.	std.	Avg.	std.	T	P-value
CRP	68.75	84.32	53.88	91.28	11.387	**0.041****
WBC	10.81	5.84	10.75	6.19	25.819	**0.032****
RBC	4.05	0.80	3.86	0.87	70.797	**0.001****
HB	11.66	2.64	11.13	2.66	61.760	0.345
HCT	34.69	7.15	33.03	7.59	67.724	0.471
Platelet	251.39	116.81	235.39	116.00	30.053	**0.008****
Neutrophil	8.50	5.45	8.91	5.89	21.787	**0.005****
Lymphocyte	1.35	1.18	1.04	0.65	16.021	**0.001****
Monocytes	0.67	0.44	0.66	0.46	4.841	0.933
Eosinophil	0.09	0.26	0.07	0.22	10.798	**0.042****
Basophils	0.05	0.07	0.04	0.05	2.912	**0.004****
RDW	16.16	3.10	15.92	3.86	1.465	0.198
MPV	8.51	1.08	8.63	1.46	25.310	0.099
Glucose	166.27	91.74	144.79	73.03	18.196	**0.001****
Urea	72.40	55.56	77.31	56.02	12.877	**0.040****
Creatinine	1.72	2.64	1.74	2.16	10.403	0.762
Ast	42.47	46.06	84.46	345.67	14.012	**0.030****
Alt	30.51	40.96	56.82	222.69	6.067	0.099
Amylase	73.77	73.33	93.09	176.97	3.653	0.119
Creatine kinase (CK)	210.85	482.84	265.79	611.35	9.161	0.109
Calcium (Ca)	9.24	9.45	8.35	1.35	6.964	0.195
Sodium (Na)	134.35	20.58	136.77	15.30	7.980	0.168
Potassium (K)	4.37	1.00	4.23	0.86	1.387	**0.048****
Chlor (Cl)	99.09	20.36	102.20	12.24	5.819	**0.033****

Table 6. *NLR and PLR analysis values in SG and CUG*

	SG	CUG	
	Avg. ± SD	Avg. ± SD	P
NLR	6.29±3.32	8.56±3.26	0.773
PLR	241.7±58.99	226.33±58.32	**0.001****

Avg. ± SD: Mean ± standard deviation; NLR: Neutral lymphocyte ratio; PLR: Lymphocyte/Platelet ratio.

Table 7. *Comparison of CUG age-SOFA score*

		Age (years)		
		Avg ± Std	t Test	P-value
SOFA score	0–5 (n: 127)	68.64±16.74	4.523	**0.001***
	6–11 (n: 68)	71.88±13.51		

Table 8. *Data of PCR results*

		SG patients (n: 195)	
		n	%
PCR result	Negative	61	31.28
	Positive	116	59.49
	No	18	9.23

Thousands of patients infected with Covid-19 are followed up in hospital services in our country. While the follow-up and treatment of these patients are being carried out, it is tough to predict patients whose general conditions get worse and who may need intensive care. While many studies in the literature analyze the demographic characteristics, clinical course, and prognosis of Covid-19 patients, we aimed to see the indicators that could predict the need for intensive care treatment. While the indication of admission to intensive care at an appropriate time allows effective use of limited intensive care beds, it significantly reduces the mortality and morbidity of patients. Hence we tried to correlate the early triage or progression of the patients with the presence of symptoms and comorbid diseases, physical, imaging, and radiological findings on admission.

In a study conducted by Li et al., among the reasons affecting the risk of death from Covid-19, three important factors were identified: male gender, age above 60 years, and presence of comorbid diseases (diabetes mellitus, hypertension, chronic respiratory failure, cancer, and cardiovascular diseases)[13]. In our study, the average age

of patients who required intensive care was seventy in both genders, and the male gender was more common. The patients' ages and existing comorbid diseases who needed intensive care were similar to other studies.

The SOFA score was significant in showing mortality and morbidity in COVID-19 patients. In a study, patients with SOFA score ≥3 had high mortality[14]. Besides, a significant correlation was found between SOFA score and gender ($p<0.05$) and between SOFA score and age ($p<0.05$)[13]. Bhatraju et al. reported that the mortality rate of COVID-19 patients over the age of 65 is higher than the rest[15]. We found the mean age of patients with high SOFA scores who required intensive care higher. This can be attributed to the presence of comorbid diseases. Hence, it can be considered that patients with Covid-19 are more commonly affected systemically if they have comorbid diseases.

In a meta-analysis conducted on 1500 patients, HT, DM, COPD, cardiovascular disease, and CVD were identified as independent risk factors in patients with Covid-19 infection. However, they found no effect on cancer, liver, and kidney disease[16]. The most common comorbid diseases we found in patients were DM, HT, Heart failure, and SVH. These comorbidities are frequently encountered in the elderly population and may increase the risk of admission to the intensive care unit. Comorbid diseases similar to the literature were observed to accompany the clinical pictures in our study. The correlation of comorbid diseases between the groups was not analyzed because the comparisons between the first day of hospitalization and the first day of intensive care could be seen as a study limitation.

Covid-19 tends to cause more severe health problems in those with comorbid diseases and the elderly. According to the report that was prepared by Wu et al., while 81% of elderly patients were mild, 14% severe, and 5% were critical; the mortality rate was reported to be between 2.5–5%[17].

In the study of Guan et al.[18], the rates regarding the severity of the disease were also very close, supporting Wu et al.[17]. They reported 80% of cases as mild to moderate, 13% as severe (dyspnea, respiratory rate ≥30/min, oxygen saturation ≤93%, $PaO_2/FiO_2<300$ and more than 50% lung within 24–48 hours involvement), 6% as critically ill (respiratory failure, septic shock, and multiple organ failure). Fever, shortness of breath, cough, and chest pain were the most common symptoms. While the symptom of shortness of breath increased significantly in patients who were taken into intensive care, the changes in other symptoms were also significant. They were seen as factors that accelerated the admission to intensive care.

In a meta-analysis of asymptomatic Covid-19 patients, Kronbichler et al.[9] reported radiological findings of lung involvement in 62.2% of the cases. The data show that the radiological imagings were valuable. In our study, the most common complaint seen in patients treated in the service on the first day was shortness of breath. CT was performed in 95.38% of these patients, non-infectious findings were observed in 19% of the patients, and radiological findings compatible with Covid-19 were observed in 81%. Approximately 25% of the patient's required endotracheal intubation during intensive care treatment. Furthermore, although some of our patients had negative PCR tests, they were diagnosed and treated with the detection of "ground glass appearance." Radiological diagnosis can prevent delay in treatment as PCR tests can produce false negative results due to non-standard techniques, kit, and test equipment errors. Since some of our patients were brought from external institutions as PCR positive, treatment was initiated in these patients without the test being studied.

Considering the results of hemogram and biochemistry, the values did not return to normal limits on the first day in the intensive care unit suggests that the clinical picture mainly affects the prognosis, not the laboratory results. In other words, the admission of patients to intensive care during the early period of hospitalization can be attributed to the severity of their clinical symptoms and the limited time of initiation of treatment. Another detail is that the duration of hospital admission after the onset of symptoms has an impact on prognosis, as well.

The prognostic value of NLR and PLR values in infectious diseases has been shown in many studies, and it is known that they may have prognostic significance even in advanced-stage cancers[19,20]. NLR and PLR values were also evaluated in Covid-19 patients since it is obvious that the hemogram parameters, which were routinely assessed and frequently controlled during the initial diagnosis, can be used to determine the severity of the disease at a lower cost. Studies show that the NLR value is significantly associated with Covid-19 disease severity and even mortality in male patients[21,22]. This study found no significant correlation between NLR and the seriousness of Covid-19 disease, which may be explained by the low sample size of our research. On the contrary, the PLR level was found to have a significant predictive significance. Qu et al. concluded that the PLR value

could be associated with cytokine storm in patients requiring lengthy hospitalization. This supports our findings and may suggest that the PLR value may show the need for an intensive care unit[23].

The main limitation of our study is the small sample size and the single-center design.

Conclusion

Hospitalization and treatment should not be delayed in elderly patients with comorbid diseases and suspected Covid-19 to reduce the need for intensive care treatment.

We believe that close monitoring of symptoms such as fever and dyspnea, careful analysis of thoracic CTs, and selective admission to the intensive care unit according to hemogram and PLR values can significantly reduce mortality and morbidity of this patient cohort.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Anthropometric Measurements and Analysis Results of Metabolic Parameters of Those with Impaired Fasting Glucose and Impaired Glucose Tolerance

Bozulmuş Açlık Glikozu ve Bozulmuş Glikoz Toleransı Olanların Antropometrik Ölçümleri ile Metabolik Parametrelerinin Analiz Sonuçları

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ABSTRACT

Aim: *Prediabetes is when the blood glucose level is between the normal value and the diabetes mellitus (DM) cut-off value. It is a metabolic disorder characterized by insulin resistance due to pancreatic β-cell dysfunction caused by primary or secondary causes. It is important due to the possibility of developing DM.*

Material and Method: *We aimed to compare anthropometric and metabolic parameters in prediabetics and patients who applied to the internal medicine clinic of Kafkas University Health Education and Research Hospital between 01.06.2018–01.09.2018 included. Prediabetic individuals were divided into three as impaired fasting glucose, impaired glucose tolerance, and combined.*

Results: *Of the 64 patients in our study, 35 were female, and 29 were male. While the age, body mass index (BMI), waist circumference, HBA1c, and homeostatic model assessment (HOMA) values did not differ significantly between the two genders, weight, height, hip circumference, waist/hip, and waist/height ratio showed significant difference (respectively p=0.040, p<0.001, p=0.040, p<0.001, p=0.003). When metabolic parameters were analyzed in prediabetic groups, HBA1c and HOMA-IR values showed statistically significant differences (p<0.001, p=0.004, respectively). While there was no difference in BMI and waist circumference from anthropometric parameters, hip circumference, waist/hip values, and Waist/Height ratio differed significantly between the genders (p=0.174, p=0.849, p=0.040, p<0.001, p=0.003 respectively).*

Conclusion: *In comparing anthropometric parameters with metabolic parameters in prediabetics, it is recommended that the waist/height value shows a significant difference between the metabolic parameters and HBA1c, HOMA values in the clinical follow-up and treatment of these prediabetic agents.*

Key words: *prediabetes; impaired fasting glucose; impaired glucose tolerance; anthropometric measurement*

ÖZET

Amaç: *Prediyabet, kan şekeri seviyesinin normal değer ile diabetes mellitus (DM) cut off değeri arasında olması durumudur. Primer ya da sekonder nedenlerle oluşan pankreas β hücre disfonksiyonuna bağlı insülin direnci ile karakterize metabolik bir bozukluk olup DM gelişebilmesi nedeniyle önem arzetmektedir.*

Materyal ve Metot: *Prediyabetiklerde antropometrik parametreler ile metabolik parametrelerin karşılaştırılmasını amaçladığımız çalışmamıza 01.06.2018–01.09.2018 tarihleri arasında Kafkas Üniversitesi Sağlık Eğitim ve Araştırma Hastanesi İç hastalıkları polikliniğine başvuran hastalar içerisinden çalışma kriterlerine uyan hastalar alındı. Prediyabetik bireyler bozulmuş açlık glukozu, bozulmuş glukoz toleransı ve kombine olmak üzere üç gruba ayrıldı.*

Bulgular: *Çalışmamıza dahil edilen 64 hastanın 35'i kadın, 29'u erkek idi. Cinsiyetler arasında yaş, vücut kitle indeksi (BMI), bel çevresi, HBA1c, homeostatik model değerlendirmesi (HOMA) değerleri anlamlı farklılık göstermez iken, kilo, boy, kalça çevresi, bel/kalça ve bel/boy oranı anlamlı fark göstermiştir (sırası ile p=0,040, p<0,001, p=0,040, p<0,001, p=0,003). Prediyabetik gruplarda metabolik parametreler analiz edildiğinde HBA1c ve HOMA-IR değerleri gruplar arasında istatistiksel olarak anlamlı farklılık gösterdi (sırası ile p<0,001, p=0,004). Antropometrik parametrelerden BMI ve bel çevresi açısından fark yok iken kalça çevresi, bel/kalça ve bel/boy oranı cinsiyetler arasında anlamlı farklılık gösterdi (sırası ile p=0,174, p=0,849, p=0,040, p<0,001, p=0,003).*

Sonuç: *Prediyabetiklerde antropometrik parametrelerin metabolik parametreler ile karşılaştırılmasında bel/boy değerinin, metabolik parametrelerden ise HBA1c, HOMA-IR değerlerinin gruplar arasında istatiksel olarak anlamlı bir farklılık göstermesi bu parametrelerin prediyabetiklerin klinik izleminde ve tedavisinde göz önünde bulundurulması önerilir.*

Anahtar kelimeler: *prediyabet; bozulmuş açlık glukozu; bozulmuş glukoz toleransı; antropometrik ölçüm*

Introduction

In the development of Diabetes Mellitus (DM), several pathogenic processes may result in insulin deficiency and resistance to insulin action, which occurs with autoimmune destruction of β cells. Prediabetes is a metabolic disorder characterized by insulin resistance due to β-cell dysfunction caused by primary or secondary causes. It is important because of the possibility of DM

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development. It is divided into three isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), and combined type (IFG + IGT)[1].

While insulin resistance is within normal limits in muscle tissue in IFG, hepatic insulin resistance starts, whereas, in IGT, insulin resistance is mainly in the muscles. Although the rate of progression of prediabetes to DM varies according to the population's characteristics and the prediabetic, DM develops in approximately 5–10% of prediabetic patients every year[2].

β-cell dysfunction is found in both isolated IFG and isolated IGT. In IFG, the early insulin response is severely impaired during the OGTT. The correlation between prediabetes and nephropathy, neuropathy, retinopathy, cognitive dysfunction, and macrovascular disease has been demonstrated in many studies[3,4].

Diabetic retinopathy (DR) is characterized by progressive vision loss, causes damage to retinal microvasculature, deterioration of the blood-retina barrier, and neovascularization, leading to vision loss[5].

In previous studies, the prevalence of chronic kidney disease (CKD) was found to be 17.7% in prediabetic individuals, 10.6% in those with normal blood glucose levels, independent of body mass index (BMI), and rate of stage 3 or stage 4 nephropathy among prediabetic patients with CKD was 56.2%[6]. Diabetic neuropathy develops in approximately 50% of DM patients, and the risk of neuropathic complications is similarly high in the presence of prediabetes[7].

In clinical practice, anthropometric measurements are often accepted as a practical and valuable approach in prediabetics and DM: Waist and hip circumference, body mass index (BMI), waist/hip, and waist/height ratios.

When insulin resistance increases, β cells increase insulin production to keep blood glucose levels within normal limits. If insulin resistance continues or increases, β cells will begin to be affected, and DM will develop by decreasing insulin secretion[8]. Although parameters predicting the development of DM in prediabetics were investigated in previous studies, it was tried to determine whether there was a difference between anthropometric and metabolic parameters in patients with IFG, IGT, and IFG+ IGT, rather than determining a predictive parameter in this study.

Material and Method

Thirty-five women who applied to the internal medicine outpatient clinic and met the determined study criteria, 64 patients, including 29 men, were recruited: those with fasting blood glucose of 100–125 mg/dl, those with an HBA1c value of 5.7–6.4%, those with a positive family history, those with BMI ≥30 were taken. Sufficient carbohydrates for a 75 g glucose load at least three days before the test (≥150 g/day), taking and maintaining daily routine physical activity, patients were included in the study with the recommendation of at least 8 hours of fasting. The time when glucose was started to be drunk in 250–300 ml of water was considered the beginning of the test.

Serum samples were obtained by centrifuging blood samples at 3000 rpm for 10 minutes. Serum glucose, lipid profile, HBA1c, and C-reactive protein (CRP) levels by Cobas c501 (Roche Diagnostics, Germany) autoanalyzer, insulin, ferritin, and vitamin D, parathormone, folic acid levels were studied with Unixel DXI 600 (Beckman Coulter Diagnostics, France). Complete blood counts were taken into tubes containing ethylenediaminetetraacetic acid (EDTA) and were performed with ABXPentra DX 120 device (Horiba, France). Waist circumference was 102 cm for men and 88 cm for women between the lower edges of the ribs and the iliac crest on a horizontal plane. Hip circumference was measured over the anterior superior spine iliaca. For BMI, it was taken by dividing the weight by the square meter of height (according to the Quetelet index). Normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2) were taken.

IFG: plasma glucose was taken as 100–125 mg/dL.

IGT: After 75 g glucose load, 2nd-hour plasma glucose is 140–199 mg/dL.

Combined: IFG+ IGT

HBA1c values: 5.7–6.4% were taken as prediabetic.

For the diagnosis of DM: Fasting plasma glucose >125 mg/dL, 2nd hour after glucose load ≥200 mg/dL or HBA1c ≥6.5%.

HOMA (homeostasis model assessment)=[fasting insulin (μu/mL) × fasting plasma glucose (mg/dL)]/405 equation[1,9]. Pregnant women, those younger than 18 years of age, those with existing diagnoses of type 1 and type 2 DM, those who refused to drink 75 grams of glucose, and those who could not tolerate 75 grams of glucose solution were not included in the study.

Statistical analysis SPSS 20.0 package program was used (SPSS Inc. Chicago, USA). Mean ± standard deviation calculated for continuous variables. Homogeneity among the four defined groups was assessed using the one-way-ANOVA test and Levene statistic. Tamhane's T2 determined significance between non-homogeneous groups, Significance between homogeneously distributed groups was investigated using the Bonferroni test. For all statistical data, $p<0.05$ was considered significant.

Ethics committee approval numbered 80576354-050-99/115 was obtained by the Ethics Committee of the Medicine faculty, Kafkas University, in the session numbered 09, dated 26.06.2018.

Results

A total of 64 patients were included in our study. Of these, 54.6% were women (n=35). The mean age of our patients was 46 in women, 48 in men, the youngest age was 20, and the highest was 77. Age, and waist circumference between men and women, There was no significant difference between BMI, HBA1c, and HOMA values. However, there were statistically significant differences in weight, height, waist/hip, waist/height ratio, and hip circumference (Table 1, p<0.05).

Although age, weight, height, waist circumference, hip circumference, and BMI did not differ significantly between prediabetic groups, HBA1c and HOMA values showed a significant difference (Tables 2 and 3, p<0.05).

The mean values of waist/height and waist/hip among the groups and statistical analysis of the groups are shown in Table 4.

The distribution of anthropometric parameters according to Hb A1 c values is shown in Table 5, and in Table 6, the measurements of anthropometric parameters according to HOMA values are compared.

Discussion

Studies show that insulin secretion is continuous during the progression from normal glucose tolerance level to DM. Although an increase in glucose levels is pursued in the first years in those who develop DM, there is an increase in blood glucose levels up to 13 years before the diagnosis [10–12].

Studies have demonstrated that insulin resistance is present in the first stage of DM and that β-cell mass and insulin secretion is increased; in the next stage, following the compensatory period, the stable adaptation process begins, in which the β-cells cannot fully compensate for the increased insulin resistance. During this period, fasting and postprandial glucose levels cannot be kept at normal levels[2,13]. This stage is attended by a decrease in acute insulin secretion when fasting, postprandial glucose levels are within the normal range, and IFG levels are around 100 mg/dL[13,14]. In the last stage of DM development, that is, glucose levels begin to increase rapidly in the decompensation period as insulin resistance cannot be compensated by β-cells[13].

Endogenous glucose production products and fasting insulin are used as markers of hepatic insulin resistance and show a strong association with fasting glycemia[11,12,15].

During glucose absorption, the blood glucose level is determined by intestinal absorption, inhibition of endogenous glucose production, and total body glucose uptake. Endogenous glucose is markedly depressed in normal glucose-tolerant humans after glucose ingestion. This suppression is less in prediabetic and diabetic individuals[11,12].

Insulin resistance and impaired β-cell function are the major defects in type 2 DM and are detectable in both IGT and IFG patients. Although investigations show that insulin resistance differs between these two diseases, those with IGT have only mild hepatic insulin resistance and significant muscle insulin resistance. At the same time, those with IFG have serious hepatic insulin resistance

Table 1. *Comparison of patients' biodemographic and anthropometric measurements by gender*

	Mean ± Std.		
	Female (N: 35)	Man (N: 29)	P
Age	46±12	48±12	0.388
Weight	76±12	87±15	0.040
Height	158±4	174±6	<0.001
Waist circumference	101±11	101±12	0.849
Hip circumference	110±11	102±10	0.040
BMI	30±4	28±5	0.174
Waist/Hip	0.91±0.05	0.99±0.38	<0.001
Waist/Height	0.63±0.06	0.58±0.07	0.003
HBA1c	5.8±1.5	6.3±1.8	0.278
HOMA	2.7±1.5	2.6±1.3	0.689

HBA1 c: Hemoglobin A1C; HOMA: Homeostatic Model Assessment.

Table 2. *Distribution of variables by disease groups*

	Groups	n:	Mean ± Std.	P
Age	IFG	24	42.63±11.32	0.052
	IGT	8	45.38±14.10	
	IFG + IGT	18	51.83±13.18	
	DM	14	51.43±9.68	
Weight	IFG	24	79.38±12.76	0.451
	IGT	8	81.38±25.00	
	IFG + IGT	18	80.50±13.25	
	DM	14	87.50±15.09	
Height	IFG	24	167.29±9.24	0.267
	IGT	8	166.63±10.83	
	IFG + IGT	18	161.67±8.81	
	DM	14	167.00±11.01	
Waist circumference	IFG	24	98.46±9.20	0.096
	IGT	8	96.38±17.98	
	IFG + IGT	18	104.22±10.90	
	DM	14	106.21±11.36	
Hip circumference	IFG	24	103.13±11.22	0.246
	IGT	8	105.63±14.77	
	IFG + IGT	18	110.28±12.07	
	DM	14	108.64±10.91	
BMI	IFG	24	28.42±4.44	0.217
	IGT	8	28.89±6.39	
	IFG + IGT	18	30.74±3.86	
	DM	14	31.58±6.02	
HBA1c	IFG	24	5.42±0.41	<0.001[a]
	IGT	8	5.46±0.57	
	IFG + IGT	18	5.60±0.56	
	DM	14	8.07±2.66	
HOMA	IFG	24	2.38±0.99	0.004[a]
	IGT	8	1.76±0.72	
	IFG + IGT	18	2.62±1.33	
	DM	14	3.79±1.96	

BMI: Body mass index, HBA1 c: Hemoglobin A1C, HOMA: Homeostatic Model Assessment, IFG: Impaired Fasting Glucose, IGT: Impaired Glucose Tolerance, DM: Diabetes Mellitus.
[a]ANOVA (Analysis of Variance) was performed to determine from which groups the p values were obtained in comparing HBA1 c and HOMA levels with four different groups. Post Hoc analysis (Tamhane's T2) was performed in this test. Differences in HBA1 c were determined between DM and IFG (p=0.016), DM and IGT (p=0.018), and DM and (IFG + IGT) (p=0.026) groups.

Table 3. *Comparison of those diagnosed with prediabetes and diabetes in terms of HBA1 c and mean HOMA values (with student's T test)*

Parameter	Diagnosis	Compared diagnosis	P
Comparison in terms of HBA1c levels	IFG (HBA1 c: 5.4%)	IGT	1.000
		IFG + IGT	0.971
		DM	<0.001
	IGT (HBA1 c: 5.4%)	IFG	1.000
		IFG + IGT	0.994
		DM	<0.001
	IFG + IGT (HBA1 c: 5.6%)	IFG	0.971
		IGT	0.994
		DM	<0.001
	DM (HBA1 c: 8.0%)	IFG	<0.001
		IGT	<0.001
		IFG + IGT	<0.001
Comparison in terms of HOMA levels	IFG (HOMA: 2.3)	IGT	0.669
		IFG + IGT	0.940
		DM	0.014
	IGT (HOMA: 1.7)	IFG	0.669
		IFG + IGT	0.437
		DM	0.006
	IFG + IGT (HOMA: 2.6)	IFG	0.940
		IGT	0.437
		DM	0.077
	DM (HOMA: 3.7)	IFG	0.014
		IGT	0.006
		IFG + IGT	0.077

HOMA: Homeostatic Model Assessment – Insulin Resistance, IFG: Impaired Fasting Glucose, IGT: Impaired Glucose Tolerance, DM: Diabetes Mellitus.

Table 4. *Waist/hip and waist/height average values by disease groups*

				95% confidence interval		
Parameter	Groups	n:	Mean ± Std.	Lower limit	Upper limit	P
Waist/hip	IFG	24	0.957±0.05	0.93	0.98	0.111
	IGT	8	0.91±0.09	0.83	0.99	
	IFG+IGT	18	0.94±0.04	0.92	0.97	
	DM	14	0.97±0.06	0.94	1.01	
Waist/height	IFG	24	0.59±0.06	0.56	0.61	0.027
	IGT	8	0.57±0.08	0.50	0.65	
	IFG+IGT	18	0.64±0.06	0.61	0.68	
	DM	14	0.63±0.07	0.59	0.68	

IFG: Impaired Fasting Glucose, IGT: Impaired Glucose Tolerance, DM: Diabetes Mellitus.

Table 5. *Comparison of anthropometric parameters according to HBA1c values*

	HBA1c	n:	Mean ± Std.	P
BMI	≥6.50	12	32.2±6.6	0.058
	<6.50	52	29.2±4.4	
Waist circumference	≥6.50	12	104.3±14.1	0.363
	<6.50	52	100.8±11.2	
Hip circumference	≥6.50	12	107.0±13.9	0.913
	<6.50	52	106.5±11.6	
Waist/hip	≥6.50	12	0.9±0.06	0.170
	<6.50	52	0.9±0.06	
Waist/height	≥6.50	12	0.6±0.09	0.329
	<6.50	52	0.6±0.07	

BMI: Body Mass index.

Table 6. *Comparison of anthropometric parameters according to HOMA values*

	HOMA	n:	Mean ± Std.	P
BMI	≥2.50	30	30.7±4.6	0.177
	<2.50	34	29.0±4.6	
Waist circumference	≥2.50	30	105.1±9.3	0.020
	<2.50	34	98.3±12.9	
Hip circumference	≥2.50	30	109.3±10.8	0.093
	<2.50	34	104.2±12.6	
Waist/hip	≥2.50	30	0.96±0.05	0.218
	<2.50	34	0.94±0.07	
Waist/height	≥2.50	30	0.63±0.06	0.020
	<2.50	34	0.59±0.07	

BMI: Body mass index.

with almost normal muscle insulin sensitivity. While both IFG and IGT decrease the first phase of insulin secretion, Studies have shown that there is deterioration in late phase insulin secretion when IGT develops[16,17].

In our study, when the waist/height and waist/hip ratios were evaluated according to gender, they were statistically significantly different ($p<0.001$ and $p=0.003$). When the waist/height ratio was analyzed regardless of gender, it was found to be statistically different between IFG, IGT, and IFG+IGT groups and those with DM ($p=0.027$).

The waist/height ratio is a sensitive, inexpensive, and non-invasive measurement and can be used to predict insulin resistance[18,19]. In the study we presented, there was no significant difference between the groups when waist circumference was evaluated. And waist/height ratio with HBA1c. The small number of cases showed a positive correlation between mean BMI and insulin level in the correlation analysis performed without any group discrimination ($r^2=0.146$). In other words, the contribution of BMI to insulin elevation was found to be 14.6%.

Abdominal fat mass causes insulin resistance and pancreatic cell damage by initiating chronic inflammation in fat tissue with the extrication of cytokines like tumor necrosis factor, IL-6, and resistin, which secrete adipokines that are thought to be hormonally active and thus affect glucose tolerance[20].

The first-line treatment for prediabetics is diet and exercise. It has been shown that the risk of DM in 3 years decreases by 58% with lifestyle changes, including diet and exercise, in individuals with IGT. It has been shown that the cumulative incidence of pathologies such as blindness (39%), end-stage kidney disease (38%), amputation (35%), stroke (9%), and coronary heart disease (8%) decrease with lifestyle changes. Pharmacological treatments are only recommended for patients who cannot reach target glucose levels with lifestyle changes[21,22].

In studies, acarbose, metformin, pioglitazone, glucagon-like peptide (GLP-1), glucosidase inhibitors, and

antiobesity that orlistat, etc., drugs have been shown to reduce the risk of developing DM in prediabetic individuals[23].

Although only lifestyle change is recommended initially in individuals diagnosed as prediabetic, if IFG + IGT coexistence with a high risk of developing DM, gestational DM history, BMI ≥35, HBA1c ≥6% are present, pharmacological treatment with lifestyle changes can be considered from the beginning[21].

The association between congestive heart failure, myocardial infarction, and coronary artery disease in prediabetics has been announced in recently reported studies[24]. Parameters of metabolic syndrome can often be identified in prediabetics a few years before the diagnosis of type 2 DM. These features can transform into advanced atherosclerotic vascular changes, usually due to impaired endothelium-dependent vasodilation, vascular smooth muscle dysfunction, and increased arterial stiffness[25].

Abdominal obesity is a risk factor for heart disease, DM, hypertension, dyslipidemia, and non-alcoholic fatty liver disease, and mortality rates are higher in individuals with abdominal obesity[15].

As a result, the study found a significant difference between the waist/height ratio, HBA1c, and HOMA groups of individuals with prediabetes. In the diagnosis and follow-up of prediabetes, where insulin resistance is thought to play a primary role, the use of central obesity associated with insulin resistance and its related anthropometric parameters in the clinical follow-up of patients will be very beneficial, and it is important to delay and prevent the progression to DM.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparing the Computed Tomography Findings of the Covid-19 PCR Positive Patients in Intensive Care Unit and PCR Negative Suspected Patients in Terms of Clinical and Laboratory Data

Yoğun Bakım Ünitesindeki Covid-19 PCR Pozitif ve PCR Negatif Şüpheli Hastaların Bilgisayarlı Tomografi Bulgularının Klinik ve Laboratuvar Verileri Açısından Karşılaştırılması

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ABSTRACT

Aim: *There has been an overload in the workload of intensive care units in the hospitals due the Coronavirus disease 2019 (COVID-19) pandemic, which started in 2019 and caused significant changes in the lives of people. In this process, it is not always easy to distinguish whether the patients followed in the intensive care unit with the suspicion of COVID-19 disease are actually infected or not. Our aim in this study was to reveal possible clinical, laboratory and computed tomography findings between polymerase chain reaction (PCR) (+) and PCR (-) patient groups followed up in the intensive care unit with a preliminary diagnosis of COVID-19.*

Material and Method: *In this study, we evaluated 83 patients who were confirmed to have COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) and 80 patients who were RT-PCR negative but clinically and radiologically suspicious for COVID-19. The CT results of the patients were classified in accordance with the categories specified by the Radiological Society of North America (RSNA). Many laboratory values, clinical progress of the disease, the source of infection and the complaints were also documented. We performed a statistical analysis of the data obtained between the two patient groups.*

Results: *The typical radiological appearance was significantly higher in the positive group while the atypical appearance was significantly higher in the suspected group (p = 0.001). There was no significant difference between the two groups in the indeterminate and negative categories. Regarding the laboratory findings, the means of the Sequential Organ Failure Assessment (SOFA) score, d-dimer, neutrophil, white blood cell, platelet, neutrophile/lymphocyte ratio (NLR) were significantly lower in the RT-PCR positive group. There was no significant difference between the two groups in terms of other laboratory findings.*

Conclusion: *In conclusion, it was determined that it was hard to distinguish the difference between these patients but there may be some clinical, laboratory and CT results that can facilitate this process.*

Key words: *COVID-19; computed tomography; intensive care unit; RT-PCR*

ÖZET

Amaç: *2019 yılında başlayan ve kısa sürede hayatımızda köklü değişikliklere neden olan Coronavirus hastalığı (COVID-19) küresel salgını, hastanelerin yoğun bakım ünitelerine de aşırı iş yükü oluşturmuştur. Bu süreçte COVID-19 hastalığı şüphesiyle yoğun bakım ünitesinde takip edilen hastaların gerçekte enfekte olup olmadığının ayrımı her zaman kolay olmamaktadır. Bu çalışmadaki amacımız, yoğun bakımda COVID-19 ön tanısıyla takip edilen PCR (+) ve PCR (-) hasta grupları arasındaki olası klinik, laboratuvar ve bilgisayarlı tomografi bulgularını ortaya koymaktı.*

Materyal ve Metot: *COVID-19 olduğu ters transkriptaz polimeraz zincir reaksiyonu (RT-PCR) ile doğrulanmış 83 hasta ile RT-PCR negatif olan, ancak klinik ve radyolojik olarak COVID-19 açısından şüpheli 80 hastayı değerlendirdik. Hastaların BT bulgularını Kuzey Amerika Radyoloji Derneği (RSNA) kategorilerine uygun olarak sınıfladık. Ayrıca birçok laboratuvar değerini, klinik olarak hastalık seyrini, bulaş kaynağını ve şikayetlerini dökümante ettik. İki hasta grubu arasında, elde edilen verilerin istatistiksel analizini gerçekleştirdik.*

Bulgular: *Tipik radyolojik görünüm, pozitif grupta anlamlı olarak daha yüksekti, şüpheli grupta ise atipik görünüm anlamlı olarak daha yüksekti (p = 0.001). Belirsiz ve negatif kategorilerde iki grup arasında anlamlı bir fark yoktu. Laboratuvar bulgularına göre, ardışık organ yetmezliği değerlendirmesi (SOFA) skoru, d-dimer, nötrofil, beyaz küre, trombosit, nötrofil/lenfosit oranı (NLR) ortalamaları RT-PCR pozitif grupta anlamlı derecede düşüktü. Diğer laboratuvar bulguları açısından iki grup arasında anlamlı fark yoktu.*

Sonuç: *Sonuç olarak bu iki hasta grubunun ayrımının güç olabileceği fakat bize yardımcı olabilecek bazı klinik, laboratuar ve BT bulgularının olabileceğini tespit ettik.*

Anahtar kelimeler: *COVID-19; bilgisayarlı tomografi; yoğun bakım ünitesi; RT-PCR*

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Introduction

Clinical, laboratory, and reverse transcription polymerase chain reaction (RT-PCR) tests are used in the first stage of the diagnosis of Coronavirus disease 2019 (COVID-19), but making the diagnosis becomes very difficult when cases are tested negative in RT-PCR test. In these situations, thorax computed tomography (CT) is used to help to make the diagnosis. In addition, it has been suggested that the sensitivity of thorax CT is higher than RT-PCR (98% vs 71%) in terms of the severity and prevalence of involvement in severe cases[1]. While peripheral, bilateral (multilobar) frosted-glass opacities (consolidation and crazy paving appearance can also accompany) can typically be seen in thorax CT, multifocal round frosted-glass opacities (consolidation and crazy paving appearance can also accompany) as well as other signs of inverted or organized pneumonia can be seen[2,3].

Many studies on COVID-19 disease have focused on the prognosis of laboratory tests such as C-reactive protein (CRP), d-dimer, neutrophil/lymphocyte ratio (NLR) and thoracic CT images until now. For example, Colombi et al. found a significant relationship between a well-ventilated lung volume and intensive care need and death in COVID-19[4]. The aim of this study was to evaluate the differences between the patients with RT-PCR positive and negative results in terms of certain characteristics. Thus, the researchers tried to understand how to use the data in hand to distinguish the suspected patients for COVID-19 pneumonia in services such as intensive care units where complicated patients receive treatment.

Material and Method

Patient Criteria

After obtaining the approval of Ankara City Hospital Ethics Committee (ethics committee number: E1-20-979), 83 patients with positive RT-PCR samples and 80 patients with negative RT-PCR samples and who were monitored for more than 24 hours in Ankara City Hospital Neurology-Orthopedic Hospital Intensive Care Unit between March 27 and June 1, 2020, were included in this study. Patients were divided into two groups as mild and severe: Mild cases were determined to have a respiratory rate of <30/min; peripheral oxygen saturation (SpO_2) > 93%; PaO_2/FiO_2 ratio ≥300 mmHg while severe cases were determined to have a respiratory rate of ≥30/min, $SpO_2 \leq 93\%$, PaO_2/FiO_2 ratio <300 mmHg.

The patient files were evaluated in terms of clinical and demographic features such as age, sex, comorbidity status, the clinic they were accepted to, mechanic ventilator usage, and the patient's laboratory values such as CRP, procalcitonin, d-dimer and thorax CT image features were recorded. RT-PCR positive cases were named as positive while RT-PCR negative cases were defined as suspected cases. It was checked whether there was a significant difference between the two groups in terms of the abovementioned values.

CT Inspections and Imaging Evaluation

CT scans were evaluated by two radiologists with 10 and 12 years of experience in thoracic CT. The imaging technique was standard for all patients, and non-contrast thorax CT was performed in the suspicion of COVID-19 pneumonia. The images were taken with GE Healthcare (USA) brand GE 128 revolution evo model multi-section CT device during the inspiration phase in the supine position. Imaging parameters were 1.3 mm collimation and 2.5 mm interval,100-120kV tube voltage 130-200 mAs, 240 mA, 1.4 pitch in the 64-section CT device. The section thickness after the reformat was 2.5mm. Thorax CT findings of the patients were defined as four groups as suggested by the Radiological Society of North America (RSNA) Expert Consensus in this study[5]:

Typical Appearance (Cov19Typ): Filling samples (± consolidation) in ground glass opacity with bilateral and peripheral intralobular lines that can accompany.

Indeterminate Appearance (Cov19Ind): Non-rounded and non-peripheral, multifocal, widespread, or one-sided ground glass opacities with no typical findings, no specific distribution.

Atypical Appearance (Cov19Aty): Isolated lobar or segmental consolidation, centrinodular nodules, cavitation, septal thickening without ground glass opacity with the absence of typical or indeterminate results.

Negative for Pneumonia (Cov19Neg): There are no CT results suggesting pneumonia.

In addition to these appearances, radiological findings (ground-glass opacities, consolidation, air bronchogram, pleural effusion, inverted halo signs)(and the distribution of findings in the lungs (unilateral, bilateral, upper lobe, middle lobe, lower lobe, peripheral, diffuse, random ecliptic) were documented and the differences between positive and suspected cases were evaluated. The thorax CT findings (such as cardiomegaly, pleural-pericardial effusion, mediastinal lymphadenopathy) apart from the lungs were also recorded.

Statistical Analysis

Descriptive statistics of the data obtained were calculated as the arithmetic mean, standard deviation (SD), median value, first (25th) and third quartile (75th) (IQR = 75th - 25th), absolute and relative frequencies depending on the type and distribution

of the characteristics and were summarized in tables. The conformity of numerical features to normal distribution was examined by Kolmogorov-Smirnov test.. The relationships between the patients' categorical characteristics, findings and their suspected and positive results were examined by Pearson Chi-Square test or the Fisher-Freeman-Halton exact test. The numerical features of patients with suspected and positive results were compared using Mann-Whitney U test. The statistical significance level was P <0.05 and the SPSS (v.25) program was used in calculations.

Results

A total of 163 COVID-19 patients hospitalized in the intensive care were included in the study. Of these patients, 80 were RT-PCR negative cases and 83 were RT-PCR positive cases. The mean age of the RT-PCR positive patients was 67 ± 13 years, while the mean age of RT-PCR negative patients was 69 ± 15 years. The duration of hospital stay was 11±9 days in both groups. It was found that the male population was higher in both groups (Table 1).

While suspected patients were not in the risk group at their admission, it was observed that the positive patients had a significantly higher rate of overseas, umrah and contact histories (p=0.001).

Regarding the laboratory findings, the means of the Sequential Organ Failure Assessment (SOFA) score, d-dimer, neutrophil, white blood cell, thrombocyte, NLR were significantly lower in the RT-PCR positive group. There was no significant difference between the two groups in terms of other laboratory findings (Table 2).

In the evaluation of the radiological images, the typical radiological appearance was significantly higher in the positive group while the atypical appearance was significantly higher in the suspected group (p = 0.001). There was no significant difference between the two groups in the indeterminate and negative categories. Common findings in COVID-19 pneumonia, such as ground glass appearance and crazy paving appearance were significantly higher in positive cases as predicted (p=0.01). Only the incidence rate of consolidation field was higher in suspected cases (p=0.005) (Table 3).

Regarding the type of involvement, it was found that diffuse or converging involvements were higher among RT-PCR positive cases, and other forms of involvements (such as lobar, segmental, etc.) were statistically

Table 1. *Contact history and pre-intensive care follow-up places in cases*

Variables	Group	N	%	p	Mean ± SD
Age					
	Suspicious	80	49.07	0.306	69.34±15
	Positive	83	50.93		67.67±13
Duration of Hospital Day					
	Suspicious	80	49.07	0.587	11.01±9
	Positive	83	50.93		11.84±9
Sex					
Male	Suspicious	49	47.6	0.614	
	Positive	54	52.4		
Female	Suspicious	31	51.7		
	Positive	29	48.3		
Contact History					
No Risk	Suspicious	65	63.1	0.001	
	Positive	38	36.9		
Risk Overseas History	Suspicious	1	33.3		
	Positive	2	66.7		
Risk: Umrah History	Suspicious	6	46.2		
	Positive	7	53.8		
Risk: Contact History	Suspicious	8	18.2		
	Positive	36	81.8		
Pre-intensive care follow-up places					
Admission to Hospital: Emergency	Suspicious	62	54.9	0.023	
	Positive	51	45.1		
Admission to Hospital: Service	Suspicious	10	28.6		
	Positive	25	71.4		
Admission to Hospital: Outer center	Suspicious	8	53.3		
	Positive	7	46.7		

found to be accompanying the RT-PCR negative cases more (p=0.001). Considering the evaluation of axial ecliptic, the incidence rate of diffuse involvement accompanied by the whole lung section involvement, was statistically significant in positive cases (p=0.009). In the lateralization category where the distribution of the lesions in both lungs was evaluated, it was found that unilateral lesions were significantly higher in suspected cases while bilateral lesions were significantly higher in positive cases (p=0.04) (Table 3).

While 60% of the positive cases were severe cases, 53% of the suspected patients were severe cases. No statistically significant difference was found in this respect. Regarding the exitus rate between the two groups, there were no statistically significant difference (Table 4).

Table 2. *Laboratory data of suspicious and positive cases*

					Percentiles			
	Group	N	Mean	SD	25	Median	75	P
APACHE Score	Suspicious	80	15.03	9.18	7.25	14.00	20.00	0.215
	Positive	83	13.22	8.30	7.00	10.00	20.00	
SOFA Score	Suspicious	80	6.20	4.09	2.00	6.00	9.00	**0.024**
	Positive	83	4.78	3.15	2.00	4.00	7.00	
Ferritin	Suspicious	75	774.11	1529.18	100.00	348.00	773.00	0.441
	Positive	83	967.66	4161.58	216.00	433.00	688.00	
C-Reactive Protein	Suspicious	80	107.46	82.03	41.50	96.50	162.00	0.904
	Positive	83	105.75	79.56	38.00	98.00	163.00	
Procalcitonin	Suspicious	80	3.50	11.61	0.08	0.27	1.16	0.065
	Positive	83	1.52	8.59	0.08	0.14	0.49	
Sedimentation	Suspicious	77	53.09	37.07	21.00	50.00	83.50	0.288
	Positive	83	57.82	33.52	30.00	55.00	84.00	
Lactate	Suspicious	80	2.40	2.07	1.39	1.78	2.40	0.165
	Positive	83	1.91	1.02	1.25	1.56	2.25	
D-dimer	Suspicious	79	6.31	8.57	1.39	2.42	6.44	**0.001**
	Positive	82	3.26	5.91	0.80	1.28	2.54	
Interleukin-6	Suspicious	63	137.89	234.91	32.00	59.70	141.00	0.157
	Positive	67	113.92	218.37	26.00	50.50	91.00	
Troponin	Suspicious	78	258.68	917.26	7.75	21.00	58.25	0.100
	Positive	82	102.45	280.09	7.00	13.50	34.75	
LDH	Suspicious	80	377.89	249.45	236.50	317.50	447.50	0.176
	Positive	83	381.17	155.06	247.00	354.00	510.00	
ALT	Suspicious	80	46.13	80.62	13.00	22.50	38.75	0.234
	Positive	83	51.10	90.00	17.00	26.00	46.00	
AST	Suspicious	80	61.81	123.27	18.00	31.50	60.00	0.161
	Positive	83	59.75	76.37	22.00	40.00	72.00	
Na	Suspicious	80	138.18	6.91	135.00	138.00	141.75	0.703
	Positive	83	138.10	5.47	135.00	138.00	140.00	
Glucose	Suspicious	80	163.50	120.70	94.75	130.50	176.00	0.681
	Positive	83	140.57	62.49	98.00	120.00	164.00	
Albumin	Suspicious	80	37.66	5.41	35.00	38.00	41.00	0.821
	Positive	83	37.61	5.37	35.00	38.00	41.00	
Lmphocyte	Suspicious	80	1.13	1.30	0.59	0.86	1.27	0.198
	Positive	83	0.89	0.55	0.52	0.80	1.10	
Neutrophil	Suspicious	80	12.23	15.80	5.70	8.83	12.10	**0.001**
	Positive	83	6.95	6.89	3.50	4.79	8.07	
WBC	Suspicious	80	12.67	10.04	7.82	10.40	14.20	**0.001**
	Positive	83	8.39	7.25	4.60	6.10	9.94	
Platelet	Suspicious	80	272.89	132.13	166.00	264.50	349.25	**0.017**
	Positive	83	225.78	93.69	158.00	221.00	279.00	
N/L ratio	Suspicious	80	14.50	16.18	5.22	9.42	18.55	**0.046**
	Positive	83	11.06	14.91	4.30	7.50	12.00	
Urea	Suspicious	80	75.01	61.37	36.25	48.00	88.50	0.150
	Positive	82	54.83	36.44	34.00	43.00	63.00	
Creatinine	Suspicious	80	1.83	2.16	0.77	1.04	1.72	0.165
	Positive	83	1.25	1.41	0.78	0.93	1.25	
GFR	Suspicious	80	62.46	35.34	29.50	65.50	89.50	**0.050**
	Positive	83	73.84	30.47	52.00	77.00	95.00	

*APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, LDH: Lactate dehydrogenase, ALT: Alanin aminotransferaz, AST: Aspartate aminotransferase, WBC: White blood count, N/L ratio: Netrophile/Lymphocyte ratio, GFR: Glomerular filtration rate.

Considering the complications, there were no complications in 98 of 163 patients. The most common complication for the two groups was acute kidney failure. Although the number was higher in suspected cases than positive cases, no statistically significant difference was found between the two groups in this respect (p=0.07) (Table 4).

Regarding the patients' complaints for the application to the hospital, it was observed that the number of patients with the complaints of fever and cough were significantly higher among positive patients (p=0.001).

Discussion

Clinical, laboratory, RT-PCR and thorax CT results are used in the diagnosis of COVID-19 disease in the present day. Despite all these criteria, there may be some patients who are difficult to diagnose, like patients with

Table 3. *Distribution of suspected and positive patients according to RSNA classification and radiological findings on thorax CT*

		Group				
		Suspicious		Positive		
		n	%	n	%	P
RSNA category	Typical	26	31.0	58	69.0	**0.001**
	Indeterminate	10	58.8	7	41.2	
	Atypical	35	77.8	10	22.2	
	Negative	9	52.9	8	47.1	
Ground glass opacity	No finding	33	63.5	19	36.5	**0.012**
	Finding	47	42.3	64	57.7	
Crazy paving pattern	No finding	44	60.3	29	39.7	**0.010**
	Finding	36	40.0	54	60.0	
Consolidation	No finding	53	54.1	45	45.9	0.117
	Finding	27	41.5	38	58.5	
Only consolidation	No finding	56	43.4	73	56.6	**0.005**
	Finding	24	70.6	10	29.4	
Reversed halo sign	No finding	80	49.7	81	50.3	0.162
	Finding	0	0.0	2	100.0	
Subpleural reticulation	No finding	38	50.7	37	49.3	0.708
	Finding	42	47.7	46	52.3	
Pleural effusion	No finding	41	47.7	45	52.3	0.704
	Finding	39	50.6	38	49.4	
Mode of involvement	No finding	10	50.0	10	50.0	**0.001**
	Scattered multiple round	8	57.1	6	42.9	
	Scattered multiple unround	15	50.0	15	50.0	
	Diffuse compound	25	34.2	48	65.8	
	Other (lobar-segmental)	22	84.6	4	15.4	
Axial involvement	No finding	9	45.0	11	55.0	**0.009**
	Peripheral	37	54.4	31	45.6	
	Diffuse	20	35.1	37	64.9	
	Central	7	63.6	4	36.4	
	Other	7	100.0	0	0.0	
Air bronchogram	No finding	53	49.1	55	50.9	0.998
	Finding	27	49.1	28	50.9	
Lateral involvement	No finding	9	52.9	8	47.1	**0.047**
	Unilateral	16	72.7	6	27.3	
	Bilateral	55	44.4	69	55.6	
Lobar involvement	No finding	8	50.0	8	50.0	0.078
	Upper lob	12	75.0	4	25.0	
	Middle lob	0	0.0	1	100.0	
	Lower lob	11	64.7	6	35.3	
	All lobes	49	43.4	64	56.6	
Additional findings	No finding	41	51.3	39	48.8	0.864
	Lymphadenopathy	7	53.8	6	46.2	
	Cardiomegaly	21	50.0	21	50.0	
	Pericardial effusion	0	0.0	2	100.0	
	Emphysema	4	36.4	7	63.6	
	Mass	1	33.3	2	66.7	
	Fibrosis	4	50.0	4	50.0	
	Lymphadenopathy + pneumothorax	2	50.0	2	50.0	

*RSNA: Radiological Society of North America, CT: Computed Tomography.

many additional problems and comorbid conditions, especially those hospitalized in intensive care units. Thorax CT appearances stand out especially in the RT-PCR negative patients with clinical and laboratory results referred to COVID-19 infection. The following questions come to mind at this stage; Is there a serious difference in thorax CT appearances of patients who are tested positive and negative for RT-PCR? Is there a thorax CT appearance or a laboratory or clinical feature that can provide specificity and sensitivity in the diagnosis of COVID-19 for RT-PCR negative patients? Can the diagnosis process be made easier for these patients? It is known that many studies were and are still conducted to answer these questions.

Table 4. *Complaint, comorbidity, treatment, and clinical progress data of the cases*

			Group				
			suspicious		positive		
			n	%	n	%	P
	Additional Germ Reproduction	No finding	53	51.0	51	49.0	0.523
		Finding	27	45.8	32	54.2	
	Clinical Condition	Mild	37	52.9	33	47.1	0.403
		Severe	43	46.2	50	53.8	
	Result	Exitus	34	47.9	37	52.1	0.789
		Discharge	46	50.0	46	50.0	
Treatment	HFN	No finding	76	52.8	68	47.2	**0.009**
		Finding	4	21.1	15	78.9	
	NIMV	No finding	75	50.3	74	49.7	0.295
		Finding	5	35.7	9	64.3	
	IMV	No finding	44	50.0	44	50.0	0.799
		Finding	36	48.0	39	52.0	
	Prone position	No finding	76	52.1	70	47.9	**0.026**
		Finding	4	23.5	13	76.5	
Comorbidity	Diabetes	No finding	51	44.7	63	55.3	0.091
		Finding	29	59.2	20	40.8	
	Hypertension	No finding	45	53.6	39	46.4	0.265
		Finding	35	44.3	44	55.7	
	Cononary Artery Disease	No finding	54	46.6	62	53.4	0.310
		Finding	26	55.3	21	44.7	
	Chronic Obstructive Pulmonary Disease	No finding	65	47.4	72	52.6	0.338
		Finding	15	57.7	11	42.3	
	Chronic Renal Failure	No finding	63	46.0	74	54.0	0.070
		Finding	17	65.4	9	34.6	
	Cancer	No finding	64	46.4	74	53.6	0.105
		Finding	16	64.0	9	36.0	
	Neurological Deficit	No finding	58	46.4	67	53.6	0.215
		Finding	22	57.9	16	42.1	
Patient Complaint	Fever	No finding	56	60.2	37	39.8	**0.001**
		Finding	24	34.3	46	65.7	
	Dyspnea	No finding	31	47.0	35	53.0	0.552
		Finding	49	50.5	48	49.5	
	Cough	No finding	54	55.7	43	44.3	**0.041**
		Finding	26	39.4	40	60.6	
	Diarrhea	No finding	79	48.8	83	51.2	0.307
		Finding	1	100.0	0	0.0	
	Weakness	No finding	58	46.4	67	53.6	0.215
		Finding	22	57.9	16	42.1	
	Nausea	No finding	72	47.7	79	52.3	0.205
		Finding	8	66.7	4	33.3	
	Anorexia	No finding	71	47.0	80	53.0	0.062
		Finding	9	75.0	3	25.0	
	Abdominal pain	No finding	78	48.8	82	51.3	0.539
		Finding	2	66.7	1	33.3	
	Complication	No finding	42	42.9	56	57.1	0.075
		Acute kidney failure	30	57.7	22	42.3	
		Multiorgan failure	3	100.0	0	0.0	
		Pneumotorax	1	50	1	50	
		Thrombosis	4	66.7	2	33.3	

*HFNO: High flow nasal oxygen, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation.

Whether patients have typical symptoms and the incidence frequency of the disease within society are the determinants for the diagnostic accuracy rates of CT in COVID-19 pneumonia. In a published case report, a 34-year-old male patient from a high-risk area applied to the hospital with a complaint of fever. While his CRP value was high, the other laboratory tests were considered normal. The nasopharyngeal RT-PCR sample taken from the patient was tested negative for four times. Irregular ground-glass opacity was observed in the patients' thorax CT scan taken as he was a suspected case, and the patient was diagnosed with COVID-19[6]. In a study conducted as if to confirm this case, the sensitivity of thoracic CT was calculated to be 90–94%, specificity was 79–84%, positive predictive value was 90%, and negative predictive value was 50–73% in patients with typical clinical findings and in the pandemic period when the prevalence is high[7]. At this point, it should be emphasized that there are studies in the literature showing that CT performed in the prone position shows more accurate results than CT performed in the supine position in patients with comorbidities[8].

In a study conducted in China, 1014 COVID-19 patients were evaluated according to their RT-PCR negative and positive results and thorax CT appearances. Of the 1014 patients, 601 (59%) were evaluated as positive with RT-PCR, and 888 (88%) were evaluated as positive by thorax CT appearances. Thorax CT appearances of 308 (75%) of the patients who were RT-PCR negative were found to be compatible with COVID-19 disease. The sensitivity of thorax CT appearances for diagnosis was found to be 97% in the study[9]. The thorax CT appearances of 26 (32%) of 80 RT-PCR negative patients were evaluated as typical in the present study. However, it must be remembered that the CT appearances of COVID-19 infection can occur due to suspected (indeterminate category) and atypical findings and even without any findings (negative category) as stated in the classification of RSNA. Therefore, the findings listed as typical for CT are not specific to COVID-19 and can be observed in many infective processes and even in non-infectious processes.

In another cohort study, 205 patients with other viral causes and 219 patients diagnosed with COVID-19 disease were compared. It was found that thorax CT appearances were more determinant than RT-PCR test to exclude COVID-19 disease. It was found that COVID-19 pneumonia was more likely to show the peripheral distribution and ground-glass opacity while thin reticular opacity, vascular enlargement, accompanying pleural effusion and lymphadenopathy were found to be less likely to be seen in the same study10. While the typical radiological appearance, especially grounded glass appearance and crazy paving appearance, was significant in positive patients, only consolidation appearance and atypical findings were statistically significant in suspicious cases in this study. These findings are consistent with previous studies, and the peripheral - diffuse distributed grounded glass opacity areas accompanied by crazy paving appearance, which sometimes forms nodular clumps and are described for COVID-19 infection, were the common CT findings obtained among the patients tested positive in the PCR test. The involvement in positive cases showing diffuse-fusion tendency was significant while lobar and segmental involvements were more significant in suspected cases. Considering the axial involvement, the diffuse involvement which spread to the whole lung area was statistically more significant in positive cases while central and other involvements were statistically more significant in suspected cases. In the evaluation of lesions distributed in the lungs, unilateral lesions were significant in suspected cases while bilateral lesions were significant in positive cases. Bilateral involvement was found to be higher in patients tested positive for COVID-19 with the PCR test in this study in line with the literature.

The thorax CT images such as lymphadenopathy, cardiomegaly, pleural effusion, pericardial effusion, emphysema, mass, and fibrosis were examined as additional findings. The most common findings in both groups were cardiomegaly and pleural effusion. The findings of the suspected and positive patients were examined one by one, and no significant difference was found. The reason for this might be that the study group included patients who were monitored in the intensive care unit and who had many additional problems and comorbid conditions. The cavitary lesion that developed in a patient followed up in the intensive care unit reminded us that we should be ready for all kinds of surprises in such patients (Fig. 1).

In another study, the characteristics of the patients who were first tested negative with RT-PCR but tested positive in the control. The probability of having a negative RT-PCR result was found to be statistically significant in patients with a thrombocyte count of more than 207×10^3 mm^3 and white blood cell count of more than 6.95×10^3 mm^3. In the same study, it was found that patients with negative RT-PCR test result at first had higher inflammation markers in the 6-day period after the onset of the symptoms than the positive cases[11]. The present study discussed the patients who were tested negative in the first RT-PCR test and were diagnosed with COVID-19 disease based on other diagnostic criteria and treated. Additionally, the RT-PCR results of these patients during follow-up were not recorded. In correlation with the current study, blood cell count and thrombocyte count were found to be lower in the RT-PCR positive group while the mean SOFA score, d-dimer, neutrophil, and N/L ratio means were found to be significantly lower. There was no significant difference between the two groups in terms of other laboratory findings.

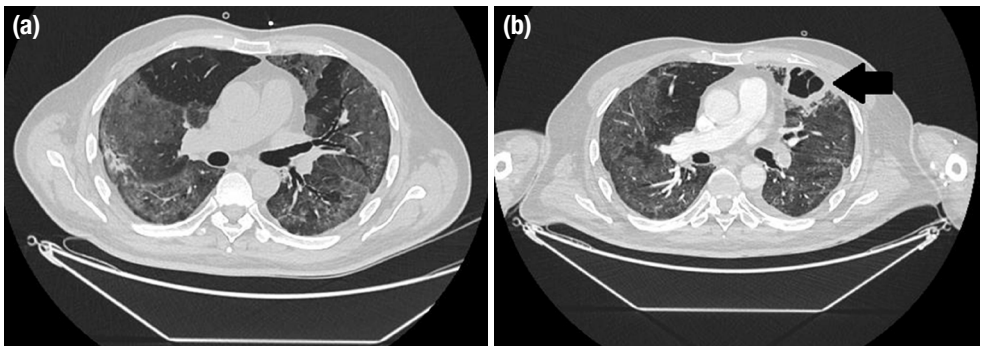

Figure 1. a, b. *A patient who was followed in the intensive care unit due to Covid-19 pneumonia and developed a cavitary lesion in the follow-up CT. Initial* ***(a)*** *and approximately one month later CT examination* ***(b****, arrow)*.

Conclusion

The specificity of the thorax CT imaging is very high for COVID-19 disease. However, it should be remembered that typical CT findings defined for COVID-19 are not specific to this disease and COVID-19 infection may manifest in some atypical presentations. The current comorbidities of the patient such as heart failure, kidney failure, immune system problems, chronic destructive lung diseases may affect the lung findings, and these diseases may also cause misunderstandings by creating CT appearances like COVID-19 pneumonia. Despite everything, there will be suspected and undiagnosed patients for COVID-19. The current knowledge on this subject must be deepened by conducting more studies and may be by using sophisticated methods such as artificial intelligence and machine learning.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethical Statement

This retrospective study has been approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki (2000).

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Effects of Engeletin on Cell Proliferation and Invasion in the Human Breast Cancer Cell Line (MCF-7)

İnsan Meme Kanseri Hücre Hattında (MCF-7) Engeletin'in Hücre Proliferasyonu ve İnvazyonu Üzerindeki Etkileri

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ABSTRACT

Aim: *Belonging to the group of flavonoids, Engeletin is a molecule with strong anti-inflammatory, antioxidant and anticancer properties. However, the effect of this molecule on breast cancer cells has not been studied yet. For this purpose, the effectiveness of Engeletin (ENG) on cell proliferation, invasion, and apoptosis in the human breast cancer cell line (MCF-7) was investigated in this study.*

Material and Method: *ENG was studied at 1, 10, and 100 μM doses in the MCF-7 cell line. In the study, cell proliferation was analyzed by MTT cell viability test, its effectiveness on invasion was analyzed by Transwell assay, and cellular viability and apoptotic evaluation were analyzed by fluorescence staining method.*

Results: *It was determined that engeletin reduced MCF-7 cell proliferation. The ENG 100 μM dose was found to be the most effective dose. While ENG application decreases the number of viable cells, it causes an increase in the number of apoptotic cells. In addition, it was determined that ENG application significantly reduced the number of invasive cells in a dose-dependent manner compared to the control group (p<0.001).*

Conclusion: *Engeletin is a molecule with anti-carcinogenic, antiproliferative activity on MCF-7 cells. In addition, ENG shows an anti-invasive activity in MCF-7 cells, demonstrating that it is a molecule with anti-metastatic activity.*

Key words: *engeletin; cell proliferation; cell viability; invasion; MCF-7*

ÖZET

Amaç: *Flovonoidler grubunda yer alan engeletin, güçlü antiinflamatuar, antioksidan ve antikanser özellikleri olan bir moleküldür. Ancak bu molekülün meme kanseri hücrelerinde etkisi henüz araştırılmamıştır. Bu amaçla bu çalışmada hücre kültüründe engeletinin (ENG) meme kanseri hücrelerinin (MCF-7) proliferasyon, invazyon ve apoptozisle olan etkisi araştırılmıştır.*

Materyal ve Metot: *MCF-7 hücre hattında ENG 1, 10 ve 100 μM dozlarında çalışıldı. Araştırmada hücre proliferasyonu MTT hücre canlılık testi ile invazyon üzerindeki etkinliği Transwell deneyi ile, hücresel canlılık ve apoptotik değerlenirilmesi ise floresans boyama yöntemi ile analiz edildi.*

Bulgular: *Engeletinin MCF-7 hücre proliferasyonunu azalttığı tespit edildi. ENG 100 μM dozu en etkin doz olduğu görüldü. ENG uygulaması canlı hücre sayısını azaltırken apoptotik hücre sayılarınında artışa neden olmaktadır. Ayrıca ENG uygulamasının doza bağlı olarak invaze olan hücre sayısını kontrol grubuna göre anlamlı şekilde azalttığı belirlendi (p<0,001).*

Sonuç: *Engeletin MCF-7 hücreleri üzerinde anti-kanserojen, antiproliferatif etkinlik gösteren bir moleküldür. Buna ilaveten ENG, MCF-7 hücrelerinde anti-invaziv bir etkinlik göstererek anti-metastatik etkinlik gösteren bir molekül olduğunuda ortaya koymaktadır.*

Anahtar kelimeler: *engeletin; hücre proliferasyonu; hücre canlılığı; invazyon; MCF-7*

Introduction

Cancer, known as the plague of the century, leads to the death of thousands of people or suffering from disease every day around the world. Breast cancer is the most common cancer in women, responsible for approximately 1 in 3 cancer types[1]. In addition, the incidence of breast cancer is increasing day by day in the world[2]. Despite the chance of success against breast cancer, technological development, advanced diagnosis and treatment options, increased social awareness, and early diagnosis in recent years, the emergence of metastatic cancer types in delayed cases cannot be prevented[3]. Although the chemotherapeutic agents cause cell death in tissue, the inability to suppress the invasion ability of the cells leads to metastatic cancers[3]. In this respect, new therapeutic

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drugs aiming to inhibit the migration of breast cancer cells may lead to the recovery of patients from the disease and increase their life expectancy and comfort.

Many native herbs have been used for medicinal purposes throughout history. Also, some chemotherapeutic drugs used for cancer treatment are extracted from plant origin, especially flowers, leaves, fruits, fungi, and lichens[4]. Moreover, some plants used in breast cancer treatment include ginseng, goldenseal, ginkgo, Echinacea, garlic, saw palmetto, and aloe vera[5]. These plants used for medicinal purposes contain aromatic-essential oils, carotenoids, and flavonoid compounds[6]. Flavonoids are a large group of heterogeneous polyphenol molecules with various health benefits[7,8]. These compounds almost find in everything from vegetables to fruits, from wine to tea; they are a large family of molecules divided into six classes consisting of flavonols (kaempferol, Quercetin), flavones (luteolin, apigenin), flavanones (naringenin, hesperidin), flavans (catechin, theaflavin), anthocyanidins (cyanidin) and isoflavones (daidzein, genistein)[9]. In recent years, research on cancer pathways such as anti-cancer[10], anti-invasion[11] ve anti-metastasis[12] has increased interest in these molecules. Engeletin, in the group of flavonoids, is a glycoside compound obtained from wine, Hymenaea martianada, Petiveria alliacea, and Engelhardia roxburghiana. Recent studies have shown that engeletin (ENG) has a strong anti-inflammatory effect[13,14]. In addition, Huang et al.[15] showed in their study that ENG is a powerful antioxidant and protects neuron cells against oxidative stress. Studies have also shown that ENG may have an anticancer effect[16]. ENG does this by inhibiting Nuclear Factor kappa B (NF-kB) in cervical carcinoma[16].

This suggests that inhibition of NF-kB[17], which is required for epithelial-mesenchymal transition and metastasis in breast cancer development, may play an anti-invasive role in breast cancer. Thus, this study was designed to investigate the possible effect of ENG on proliferation, apoptosis, and invasion of MCF-7 cells in cell culture was investigated in this study.

Materials and Methods

The cell culture, cell viability, and invasion tests of this study were carried out in the Central Research Laboratory of Kafkas University.

Preparation of MCF-7 Culture Medium

The human MCF-7 breast cancer cell line was obtained from the ATCC (American Type Culture Collection). The cancer cell line was incubed at 95% humidity and 5% CO_2, and 37°C temperature. It was fed in Dulbecco's modified Eagle's medium (DMEM, Gibco, Thermo Fisher Scientific) consisting of 10% Fetal bovine serum (FBS, Gibco, Thermo Fisher Scientific) and 1% antibiotics (Penicillin, Streptomycin, Amphotericin, Gibco, Thermo Fisher Scientific). The medium was renewed every 24 hours until the cells reached the desired numerical density in the culture medium. Cell count was calculated manually using a toma slide. For calculation, cells were first removed with the trypsin enzyme. Then, at the end of the centrifugation process, the remaining cells on the tube wall were collected in a 1 ml medium. Finally, 10 µl cells and 10 µl 0.2% Trypan blue dye were mixed in a tube, and 10 µl of the mixture was added to a toma slide and calculated. Engeletin (CAS Number: 572–31–6, MedChemExpress, USA) was applied to the cells at concentrations of 1, 10, and 100 µM.

Cell Viability Test

The antiproliferative effects of Engeletin on MCF-7 cells were investigated by MTT method[18]. After determining the appropriate doses, cells were cultered into a 96-well plate. After 24 hours, different concentrations of ENG were applied to the cells. In this study, the 3-(4.5-dimetiltiyazol2-yl)-2.5-difeniltetrazolyum-bromür (MTT) (CAS Number: M5655, Sigma, Germany) method was applied to the cells 24 hours after the application of Engeletin[19], Then, absorbance values at 570 nm wavelength were calculated with a microplate reader spectrophotometer (Thermo Scientic Multisican, Singapore). Cell viability rates were analyzed by comparison with control wells.

Fluorescent Staining Method

Twenty-four well plates were seeded as 2.5×10^4 cells in 200 µL medium for each well plate. At the end of the standard 24-hour incubation, the medium was withdrawn and washed twice with PBS. Then, 4% formaldehyde (200µL) was added to all wells for fixation and incubated for 4 minutes at room temperature. At the end of the time, formaldehyde was removed by washing with PBS. To ensure the permeabilization of the cells, 99.9% methanol (200µL) was added to the wells and kept at room temperature for 20 minutes. It was again washed with PBS. Fluorescent diacetate (FDA) was dissolved in 1 mg/mL dimethyl sulfoxide (DMSO). Propidium iodide (PI) was dissolved in 1

mg/mL purified water 5µL of PI and FDA were added to each well and visualized with an inverted microscope (Invitrogen Evos FL) with fluorescence attachment after 10 minutes of incubation.

Transwell Invasion Test

The invasion abilities of MCF-7 cells were tested with a Transwell (Corning Incorporated NY, USA) plate. This test procedure was performed as follows. Transwell wells with custom membrane 8 microns a pore width were placed in a 24-well cell plate. Matrigel solution (BD, Bioscience) was added to the membranes and incubated for 16 hours. Before transferring cells to Transwell wells, they were kept in a serum-free medium for 12 hours. After counting from the stock cell solution, cells (2.5×105 in 1 mL) were seeded into Transwell wells, including a 200 µl serum-free medium. 750 µl medium containing 10% Fetal Bovine Serum (FBS) was placed in the well under the Transwell well. Afterward, ENG 1, 10, and 100 µM doses were applied to the Transwell wells for the drug groups, and the plate was left to incubate at 37°C for 16 hours. At the end of the incubation, the medium in the Transwell wells was removed and after washing twice with PBS (Phosphate Buffer Saline). Then, 3.7% formaldehyde was added to the wells to fix the cells in the Transwell. After 2 hours, formaldehyde was removed, and 99.9% methanol was added for cell permeabilization in the Transwell. At 20 minutes, methanol was withdrawn, the Transwell wells were washed twice with PBS, and 0.1% Crystal Violet (200 µl) (Sigma Aldrich, Germany) dye was applied[20]. Traswell wells, kept in the dark for 15 minutes, were washed with PBS and cleaned with a sterilized cotton swab. Then, cells in the invading traswell membrane were counted and pictured with a light microscope (Zeizz Primostar). Graphs were drawn according to the average cell numbers, with three replicates for each group.

Statistical Analysis

Statistical analyses were performed with SPSS 20.0 software (IBM, USA), and standard error bars were added to the graphs. Analysis results were done with one-way ANOVA and Tukey multiple comparative tests. Significant differences were determined by comparing all groups among themselves. If the character used in the columns are the same, they are statistically insignificant; if they are different, they are statistically significant ($p<0.05$)

Results

Cell Viability

According to the results of the cell proliferation MTT test, it was found that there was a significant increase in the cells of the control group after 24 hours ($p>0.05$). On the other hand, ENG administration significantly reduced the number of MCF-7 cells ($p>0.05$). The best effective dose of ENG was determined as 100 µM (Fig. 1).

Results of Fluorescent Staining

According to the results of fluorescence staining, which investigated the antiproliferative and apoptotic effects of engeletin on MCF-7 cells, it is seen that the viability of MCF-7 cells in the control group is quite high (Fig. 2). In the ENG-administered groups, it is seen that the number of living cells decreases while the number of apoptotic cells increases. Depending on the dose, engeletin has been shown to have an antiproliferative and apoptotic effect on MCF-7 cells, and the best effect is shown at a dose of 100 µM (Fig. 2).

Transwell Invasion Results

Transwell wells invasion test results are shown in Fig. 3. It was found that MCF-7 cells in the control group were more invasive to the membrane base compared to other groups. As shown in Fig. 4, it was determined that ENG administration significantly reduced the number of invasive cells depending on the dose compared to the control group ($p<0.001$). When the ENG groups were compared, it was seen that the number of cells in the ENG 100 µM group was significantly less than in the other groups ($p<0.001$).

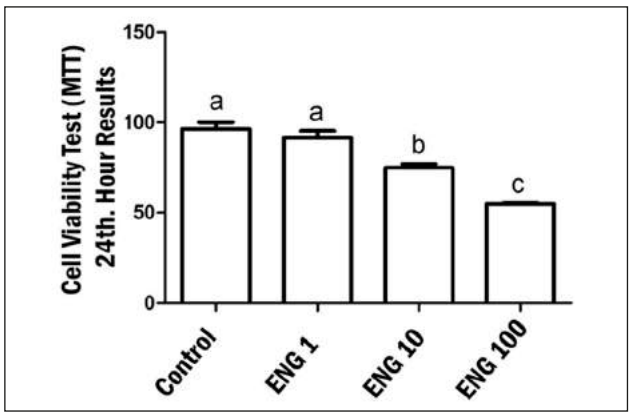

Figure 1. *Cell Viability Test (MTT) 24th hour results.*

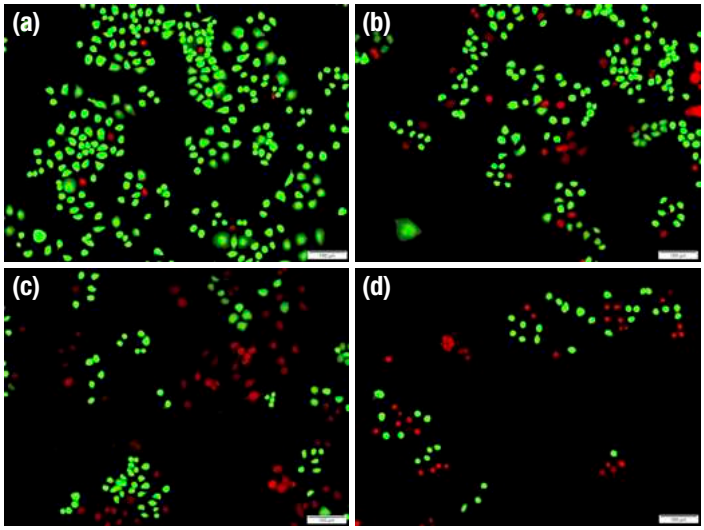

Figure 2. a–d. *FDA and PI fluorescent staining findings (**a:** Control group, **b:** ENG 1 Um group, **c:** ENG 10 Um group, **d:** ENG 100 Um group, red cells: PI (apoptotic cells), green cells: FDA (healthy cells), magnifications: 10×).*

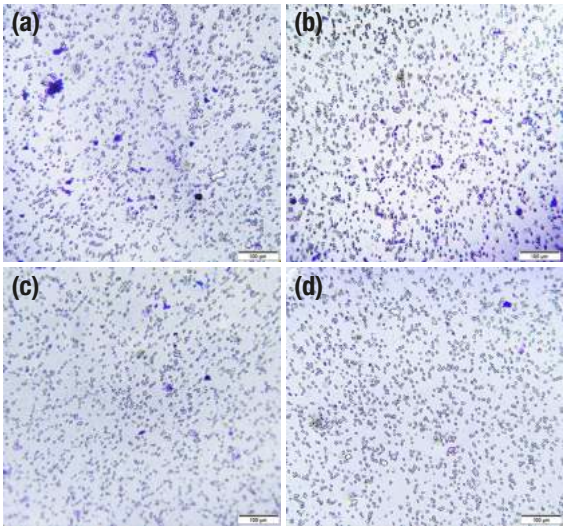

Figure 3. a–d. *Transwell membrane invasion images (**a:** Control group, **b:** ENG 1 Um group, **c:** ENG 10 Um group, **d:** ENG 100 Um group).*

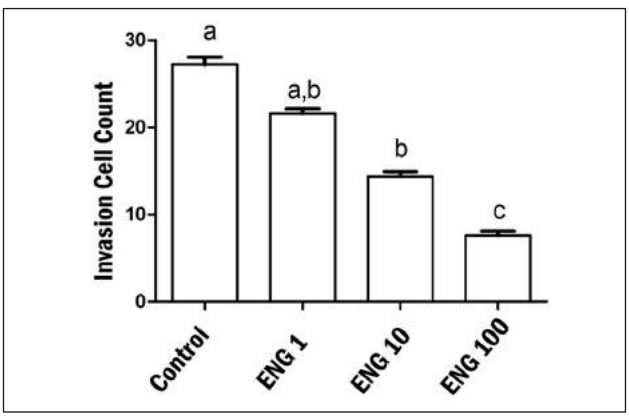

Figure 4. *Findings of Transwell membrane invasion cell count.*

Discussion

Metastasis is defined as moving to another area at the end of the body in certain conditions and processes of cancer cells, difficulties in clinical treatment with adverse effects on other tissues and organs in cancer patients. Unfortunately, metastasis is also seen in breast cancer[21]. Moreover, metastasis is responsible for most of the deaths from breast cancer[22]. This feature of breast cancer cells stems from their ability to invade. From this point of view, it can be a treatment protocol for suppressing the invasion abilities of cancer cells, especially in early cancer treatments. Thus, adding anti-invasion properties to existing chemotherapeutic drugs may support the development of new generation drugs.

Recent studies, the trial of natural biological products in treating many diseases, reveal the potential of such compounds[23,24]. Flavonoids, at the top of these molecules, have been reported as potential anti-tumor compounds by inducing apoptotic cell death, oxidative stress, and ER stress[25]. ENG, which is from the group of flavonoids, has anti-inflammatory[13,14], anti-antioxidant[15], and anticancer effects[26]. However, there are no studies on ENG's anti-proliferative and anton human breast cancer cells.

For this purpose, we first performed the MTT assay to test the antiproliferative effect of ENG on MCF-7 cells. The MTT assay measures cellular metabolic activity, indicating cell viability, proliferation, and cytotoxicity. This colorimetric method is based on converting yellow tetrazolium salt, an MTT solution, into purple formazan crystals by living and active cells. This test, one of the most preferred tests in cell culture studies, is used to test the effectiveness of active substances in cell culture. In a study investigating ENG activity on lung cancer cells, similar to our study, the MTT method was used, and its antiproliferative activity was demonstrated[26]. Another study by Wungsintaweekul et al.[27], showed that ENG has antiestrogenic activity. MCF-7 breast cancer cells are estrogen receptor-positive cells. Therefore, Briand et al.[28] has been shown that MCF-7 cells are sensitive to estrogen and antiestrogenic substances reduce the proliferation of MCF-7 cells. This important condition contributes to its antiproliferative effect on MCF-7 cells, as the blocker has antiestrogenic activity.

In our study, we applied the fluorescent staining method to show the apoptotic effect of ENG in MCF-7 cells. This method, widely used to test cell viability, is based on staining target cells with various fluorescent dyes. FDA, one of these dyes, passes passively through the phospholipid bilayer of the cell and gives a green glow in fluorescence microscope[29]. Another important dye we use is PI. Unlike FDA, PI cannot cross the undamaged plasma membrane and can only bind in the DNA of cells where the plasma membrane is compromised/permeable. These cells, seen as red in the fluorescence microscope, give us information about the cells that started the apoptotic cascade[30,31]. In our findings, while intense FDA-positive cells detected high viability in the culture medium in the control group, it was determined that these FDA-stained cells decreased in the ENG applied groups. On the other hand, the shines of PI dye in ENG applied groups proves that ENG is apoptotic and anticancer. In a study on nanoparticles on MCF-7 cells, the viability and apoptotic properties of MCF-7 cells were tested, as we observed in our findings[32]. This result confirms the method and findings of our study. These also results explain the ENG anti-proliferative effect that we observed in our MTT results by apoptosis mechanism.

In recent years, research on the mechanism underlying the invasion abilities of cancer cells and the inhibition of this metastatic cellular behavior has attracted much attention. One of these research methods, the Transwell cell invasion test method, is based on measuring the chemotactic ability of cells against an attractive chemical[33]. In our research, we tested the invasion effect of ENG on MCF-7 cells with this method. In our findings, MCF-7 cells invaded the Transwell membrane base more in the control group compared to the other groups. This result explains the metastatic behavior of MCF-7 cells. In the study of Li et al.[34], in which they investigated the effectiveness of calicosine substance on invasion and migration in human breast cancer cells, they showed that MCF-7 cells significantly penetrated the traswell membrane. This study supports our result. When ENG was applied to MCF-7 cells, it was determined that the number of invasive cells decreased significantly compared to the control group, depending on the dose. This result reveals that blockade on MCF-7 cells can show an anti-invasive effect.

A study by Bai et al.[16], determined the anti-invasive effect of ENG through NF-κB inhibition in cervical carcinoma cells. Moreover, in another study by Wu et al.[35], they showed a role in the inhibition of NF-kB via TLR4 in the lipopolysaccharide-induced endometriosis model; this explains the reason for the anti-metastatic activity of the ENG.

Engeletin is a molecule with anti-carcinogenic, antiproliferative activity on MCF-7 cells. In addition, it has been an anti-invasive activity on MCF-7 cells and anti-metastatic activity. In conclusion, it is important to prevent metastasis in breast cancer. In this respect, ENG may be a chemotherapeutic drug that can be used to treat breast cancer.

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Conflicts of Interests

The authors report no conflicts of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Did the COVID-19 Pandemic Affect the Approach to Testicular Torsion Cases?

COVID-19 Pandemisi Testis Torsiyonu Vakalarına Yaklaşımı Etkiledi mi?

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ABSTRACT

Aim: *The COVID-19 pandemic affects the approach to emergency pathologies as well as in many diseases. Testicular torsion is a scrotal emergency in which the time leading up to diagnosis and treatment is most important for organ protection. We planned to compare the time until diagnosis and treatment and the rate of organ loss between the pre-pandemic and pandemic periods in our clinic.*

Material and Method: *In our retrospective study, we included patients aged >1 year who were diagnosed with testicular torsion and treated at our clinic between March 2019 and March 2021. Patients were divided into two groups according to the time of admission. We named the period between March 2019 – March 2020 Group 1 and the interval between March 2020 – March 2021 as Group 2. We compared the two groups in terms of demographic data, ischemic duration, and orchiectomy rates.*

Results: *Of the 55 cases that met the study inclusion criteria, 26 occurred during the pre-pandemic period and 29 during the COVID-19 crisis period. The median age of the patients in Group 1 was 17 (IQR: 6–32) and that of the patients in Group 2 was 15 (IQR: 6–28) years (p=0.019). incidence of orchiectomy in our center was 31% in the Group 2 and 15.4% in the Group 1, which was not statistically significant (p=0.173). In the evaluation of the whole cohort (n=55) according to early (before 12 h) and late admission (after 12 h), the rate of orchiectomy at early admission was found to be significantly lower (50% compared to 3.6% ; p=0.006). The median time from symptom onset to first presentation was not significantly different between group1 and 2 (p=0.439).*

Conclusion: *Time to presentation, ischemic times, and orchiectomy rates for testicular torsion at our center were not significantly different during the COVID-19 period compared with the pre-pandemic period.*

Key words: *acute scrotal pathologies; COVID-19 pandemic; testicular torsion*

ÖZET

Amaç: *COVID-19 pandemisi birçok hastalıkta olduğu gibi acil patolojilere de yaklaşımı etkilemektedir. Testis torsiyonu önemli bir skrotal acil olup tanı ve tedaviye kadar geçen zaman organ korunmasında en önemli prediktif faktördür. Biz de kliniğimizde tanı ve tedaviye kadar geçen sürenin ve organ kaybı oranlarının pandemi öncesi dönemle pandemi süreci arasında karşılaştırılmasını planladık.*

Materyal ve Metot: *Retrospektif çalışmamıza kliniğimizde Mart 2019 – Mart 2021 tarihleri arasında 1 yaş üzeri testis torsiyonu tanısı alıp tedavi gören hastaları dahil ettik. Hastaları başvuru zamanlarına göre 2 gruba ayırdık. Mart 2019 – Mart 2020 aralığını (COVID-19 öncesi) Grup 1 ve Mart 2020 – Mart 2021 aralığını da (COVID-19 dönemi) Grup 2 olarak isimlendirdik. İki grubu demografik verileri ile iskemik süreleri ve orşiektomi oranları açısından karşılaştırdık.*

Bulgular: *Çalışmamıza dahil etme kriterlerini karşılayan toplam 55 hastanın 26'sı Grup 1 ve 29'u Grup 2'ye dahil edildi. Grup 1 için ortanca yaş ortalaması 17 (Inter Quantile Range (IQR): 6–32) iken grup 2'de 15 (IQR: 6–28) olarak saptandı (p=0,019). Pandemi dönemi orşiektomi oranı (%31) öncesine göre (%15,4) fazla olsa da istatistiksel anlamlılık izlenmedi (p=0,173). Tüm kohortun (n=55) erken (12 saat öncesi) ve geç başvuru (12 saat sonrası)'ya göre değerlendirilmesinde ise erken başvuruda orşiektomi oranı anlamlı olarak daha düşük saptandı (%17,8'e kıyasla %50; p=0,045). Grup 1 ve Grup 2'de erken ve geç başvuru açısından farklılık izlenmedi (p=0,439).*

Sonuç: *COVID-19 pandemisinin testis torsiyonuna olumsuz etkilerini başvuru süresi, başvuruda gecikme ya da orşiektomi oranları bakımından inceledik ve pandemi öncesi 1 yıllık dönemdeki vakalarla arasında bir farklılık saptamadık.*

Anahtar kelimeler: *akut skrotal patolojiler; COVID-19 pandemisi; testis torsiyonu*

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Introduction

Testicular Torsion (TT) occurs when the testicle rotates around the spermatic cord attachments, which obstructs blood flow and causes tissue ischemia. TT remains the most important cause of testicular ischemia and organ loss in adolescents and young men[1].

Intervention in the first 6 h after admission has been associated with minimizing organ loss, and some studies have indicated that it is possible to preserve the testis for up to 16 h. However, in the literature, it is stated that the loss of organs will be two-thirds or more in cases exceeding 12 hours[2–5]. survival testis rate in applications with TT, where timing is critical to the results, varies widely from 30% to 70%[6–8].

This study aimed to treat TT cases within the optimum time in accordance with well-defined standard treatment protocols from the diagnosis stage. Any epidemic that may affect the health system may involuntarily affect adherence to protocols in emergency cases[9].

The COVID-19 pandemic has increased in our country especially since March 2020, as it has significantly affected the health system worldwide. The current literature shows that the avoidance of admission in emergency cases unrelated to the COVID-19 pandemic has increased, and this avoidance includes many disease groups, including all age groups and life-threatening ones[10–13]. General restrictions and avoidance of the risk of transmission by the community were effective in decreasing emergency service admissions, but the difficulties brought by the pandemic to the health system caused delays in non-COVID-19 emergency cases in many countries[14,15].

The first COVID-19 case in Türkiye was detected on March 11, 2020. Since then, various restrictions have been imposed throughout the country. In particular, as a result of the decision to continue school lessons with distance education, adolescent children going out to the street were restricted. The health system, especially the pandemic hospitals, had to close their services and operating rooms during the peak periods of the epidemic, except for emergency cases. Routine and elective surgeries in our clinic were not performed during the COVID-19 period, except for a period of a few months.

In this study, we aimed to compare the COVID-19 pandemic period patient group and the pre-pandemic cohort in terms of these predictive time parameters, assuming that the COVID-19 pandemic may affect the onset of symptoms and the duration of diagnosis and operation in TT patients.

Materials and Methods

Our study was designed as a single-center retrospective study following the approval of the Medipol University non-interventional ethics committee (XXXXX) and the Scientific Research Platform approval of the Ministry of Health General Directorate of Health Services. Patients who underwent surgery in our clinic between March 2019 and March 2021 with a diagnosis of TT and were older than 1 year were included in the study.

The hospital operating system (HIS) and ICD-10 diagnosis code (N44.00=testicular torsion) were used to identify the patients. In addition, the files of the patients were reviewed retrospectively, and those who underwent surgery for TT were included in the study. Undescended testicular torsion surgery, elective fixation surgery, appendix testicular torsion, and patients younger than one year of age were excluded from the study. In addition, cases within the controlled normalization periods– periods of partially lifted restrictions (June-September 2020 and October-November 2020) during the pandemic process–were also excluded from the study.

We named the cases that occurred in the pre-COVID-19 period (March 2019 – March 2020) as 'Group 1' and compared them with the case group seen during the COVID-19 crisis period –excluding normalization periods– (March 2020 – March 2021), called 'Group 2' .

Demographic and clinical information of the patients included in the study was obtained from the "HIS," our hospital electronic data system. Both groups were compared in terms of time from symptom onset to diagnosis, time from symptom onset to operation, and orchiectomy rates. In addition, groups were compared according to whether the time to operation was >12 h or <12 h, and whether the time from symptom onset to operation was >6 h or <6 h. The time from symptom onset to diagnosis was determined according to the history taken from the patient or family, from the time of diagnosis in our clinic, or in the emergency department of the external center. The time to the operating room after diagnosis was calculated based on the operation start time recorded from the HIS electronic data system.

Finally, two groups were formed as early (<12 h) and delayed (>12 h) according to the duration of hospital admission, and age, orchiectomy rate, and hospital stay between the groups were compared.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences version 22.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are defined using frequency distributions. Mann-Whitney U, chi-square, and Fisher's exact tests were used to compare continuous and categorical variables between time periods. Continuous and categorical

data of the patients are presented as median and min-max. Statistical significance was set at P<0.05.

Results

The mean age of the 55 TT patients included in the study was 16 (6–32) years. 26 of the patients belonged to Group 1, and 29 of them belonged to Group 2. The clinical and demographic data of the patients are summarized in Table 1.

The median age was 17 (IQR 6–32) in Group 1 and 15 (IQR 6–28) in Group 2 (p=0.019). There was no statistical difference between the groups in terms of median time from symptom onset to diagnosis (Group 1:3 hours (IQR 2–48) and Group 2:3 hours (IQR 1–48); p=0.503). Similarly, no difference was observed between the groups in terms of the median time from symptom onset to operation (Group 1:6.5 hours (IQR 3–51) and Group 2:6 h (IQR 2–51); p=0.912). Although the rate of orchiectomy was higher in Group 2 than group 1, no statistical difference was observed (Group 1:4/26 [15.4%] and Group 2:9/29 [31%]; p=0.173). There were 13/26 (50%) and 14/29 (48.2%) patients in Group 1 and Group 2, whose time from baseline to operation was longer than 6 h, and no statistical difference was observed between the groups. There was no statistical difference between the groups, even if this time was longer than 12 hours (Group 1:4/26 (15.4%) and Group 2:6/29 (20.7%); p=0.173). There was no statistical difference between the length of hospital stay during the pandemic period (15 hours [IQR 3.20]) and the period before the pandemic (14 hours (IQR 5–20)] (p=0.487) (Table 2). The orchiectomy rate of the delayed group with a hospital admission time of >12 hours was found to be statistically significantly higher (>12 hours group: 5/50 (50%) and <12 hours group: 8/45 (3.6%), p=0.006; Z=-2.747). There was no statistically significant difference between the groups in terms of age and length of hospital stay in these two groups (p=0.991 and 0.130, respectively) (Table 3).

Discussion

Along with the whole world, the COVID-19 epidemic in our country, especially after March 2020, has brought innovations and new burdens to the social life and health system. The functioning of the health system has undergone changes such as postponing elective cases and allocating services and intensive care units, mainly for patients with COVID-19 pneumonia.

Many studies have been designed on the assumption that the diagnosis and treatment delay of acute pathologies is a result of the compulsory impact of the pandemic on the health system. While some studies emphasize the delay effect of the pandemic on acute cases, some studies have shown that it has no negative effects[11–13,16–21]. Contradictory results were associated with whether symptoms could be bypassed with simple treatment. The reasons for the delay were related more to the fear

Table 1. *Demographic and clinical characteristics of the patients (n=55).*

Age (years, median, range)		16 (6–32)
Side (n, %)	Right	29 (52.7)
	Left	26 (47.3)
Case time (n, %)	Group 1	26 (47.3)
	Group 2	29 (52.7)
Procedure (n, %)	Open surgery	55 (100)
Time from symptom onset to diagnosis (hours) (median [IQR]{range})		3 (1–48)
Time from symptom onset to operation (hours) (median [IQR]{range})		6 (2–51)
Orchiectomy (n, %)		13 (23.6)
Length of hospital stay (hours) (median [IQR]{range})		15 (3–22)

Table 2. *Comparison of parameters between pre-COVID-19 pandemic and COVID-19 pandemic-period groups.*

	Group 1 (n=26)	Group 2 (n=29)	p-value
Age (years, median, range)	17 (6–32)	15 (6–28)	***0.019****
Time from symptom onset to diagnosis (hours) (median [IQR]{range})	3 (2–48)	3 (1–48)	0.503*
Time from symptom onset to operation (hours) (median [IQR]{range})	6.5 (3–51)	6 (2–51)	0.912*
Orchiectomy, n (%)	4 (15.4)	9 (31)	0.173**
Time to operation ≤12 hours, n (%)	22 (84.6)	23 (79.3)	0.439**
Time to operation >12 hours, n (%)	4 (15.4)	6 (20.7)	
Time from symptom onset to operation ≤6 hours, n (%)	13 (48.3)	15 (51.7)	0.898**
Time from symptom onset to operation >6 hours, n (%)	13 (50)	14 (50)	
Length of hospital stay (hours)	14 (5–22)	15 (3–20)	0.487*

* The Mann-Whitney test, ** Chi-square test.

Table 3. *Parameter differences between Acute (≤12 hours) and delayed (>12 hours) groups*

	Acute (≤12 hours) (n=45)	Delayed (>12 hours) (n=10)	p-value
Age (years, median, range)	16 (6–32)	16 (6–30)	0.991*
Orchiectomy, n (%)	8 (3.6)	5 (50)	0.006**
Length of hospital stay (median [IQR]{range})	15 (3–22)	16 (12–20)	0.130*

* The Mann-Whitney test, ** Fisher's Exact Test

of transmission of infection by the patients or the parents rather than the change in the functioning of the healthcare system[17]. Lange et al.[13] reported a 23% (MI), 20% (stroke), and 10% (hyperglycemic crisis) decrease in admissions to the emergency department in the USA during the pandemic period.

In a study where we compared the ischemic time and organ loss rates of TT cases before and during the pandemic, we found no statistical difference. The time from symptom onset, which is critical for testicular loss, to diagnosis and surgical intervention were found to be similar in both groups. Although both orchiectomy rates and the percentage of admissions exceeding 12 hours were higher in the COVID-19 period, the lack of statistical difference may be related to the low power of the cohort, but it was interpreted in favor of not delaying, as in similar studies[15,22,23]. Although Sarah et al.[15] found that ischemic time was longer during the pandemic period, they did not find statistical significance in terms of organ loss. In a study by Tankel et al.[10], the decrease in AA (Acute Appendicitis) cases during the pandemic process was attributed to the resolution of uncomplicated cases at home with simple symptomatic treatment. A similar resolution chance may be valid for torsion that recurs and resolves spontaneously, but it is less likely to delay admission in stable cases[22,23].

In our study, we were based on the number of cases in a one-year period, and TT cases were detected slightly more frequently in the pandemic period. This situation may be related to the shift of primary and secondary healthcare services to tertiary hospitals, especially when surgery is required, or may be directly related to the increase in the number of tertiary referrals among patients. We believe that direct applications did not increase the ischemic time due to transfer, resulting in no delay during the pandemic period. The strong and rapid onset of the disease and the inability of parents to resort to relaxing and prolonging manipulations in children may be related to the short ischemic period. Delaying acute pathologies in adult patients has been found to be associated with fear of contagion[13], and the belief that a similar risk is less likely in pediatric patients also increases the possibility that they can be applied to the emergency department without hesitation for children[22]. The fact that there was no difference between the two terms regarding the application period in our study is consistent with these assumptions.

The rate of orchiectomy was significantly lower in the early admissions (<12 h) group (p=0.045). Gold et al. attributed testicular rescue after torsion to two main factors: fast and efficient in-hospital management with rapid medical intervention[24]. Including patient and parental awareness education as a third factor was found to be significant in terms of ischemia time until diagnosis[25,26].

Some factors made our study strong and weak. In particular, especially during the COVID-19 pandemic period and before, with one-year periods and the number of patients close to each other, offered a more homogeneous comparison compared with studies with similar hypotheses in the literature. In addition, we designed a study that deals with the cases of the pandemic period for the longest period of time, unlike the short periods of 1–3 months in other similar studies[15,22,23]. However, our retrospective and observational study, single-centeredness, and limited number of patients can be stated as our important limitations. Although this was a single-center study, we think that the dense and immigration-based heterogeneous population of the region addressed by our 3rd level clinic represents the general country sample. Another limitation is that the advanced prognosis of the patients who were successfully detorsion and fixed was not determined, and the rate of atrophy was insufficient. We aim to continue the study with future findings.

Our findings showed that the COVID-19 pandemic did not affect the duration of hospital admission, time from admission to exploration, and rate of orchiectomy in patients with acute TT. However, the pandemic continues to have an impact on society and the health system with increasing variant strains despite intensive vaccination programs and restrictions. In the upcoming period, training programs and information can be planned to maintain the current algorithm in emergency services and to reduce the hesitancy of the society in applying to the health center in acute cases.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Sacroiliac Joint Variations on Magnetic Resonance Imaging in Patients with Low Back Pain

Bel Ağrısı Olan Hastalarda Manyetik Rezonans Görüntülemede Sakroiliak Eklem Varyasyonları

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ABSTRACT

Aim: *To investigate the frequency of anatomical variations on the sacroiliac joint (SIJ) and reveal their clinical importance by distinguishing the findings that mimic sacroiliitis in patients referred to magnetic resonance imaging (MRI) for low back pain.*

Material and Method: *This retrospective study included all SIJ MRI examinations performed in our hospital with patients ≥18 and <65 years of age for 24 months. According to the Assessment of Spondyloarthritis International Society (ASAS) criteria, data collection consisted of the patients' age at the imaging time, gender, and the presence of active and chronic sacroiliitis. Lumbosacral transitional vertebra (LSTV) was classified according to the Castellvi classification system. Moreover, all images were assessed for the presence of major sacroiliac joint variations described in the literature. Structural and edematous changes were also noted.*

Results: *1020 MRI examinations were included, and SIJ variations were identified in 323 of them. The frequency order of anatomical variants of SIJs are as follows: 1) LSTV (114 patients, 12.2%), 2) Accessory sacroiliac joint (80 patients, 7.8%), 3) Iliosacral complex (66 patients, 6.4%), 4) Sacral defect (61 patients, 5.9%), and 5) Isolated synostosis (2 patients, 0.2%). Structural and edematous findings were frequently observed in LSTV and accessory SIJ.*

Conclusion: *We conclude that the lumbosacral transition segments and various anatomical SIJ variations are common in the low back pain population, especially in women. Moreover, these variations may be associated with degenerative and edematous signal intensity changes that mimic sacroiliitis.*

Key words: *magnetic resonance imaging; sacroiliac joint; anatomy; low back pain*

ÖZET

Amaç: *Bu çalışmada, bel ağrısı nedeniyle Manyetik Rezonans Görüntüleme (MRG)'ye başvuran hastalarda sakroiliyak eklemin (SİE) anatomik varyasyonlarının sıklığını araştırmak ve sakroiliiti taklit eden bulguları ayırt ederek klinik önemini ortaya koymak amaçlanmıştır.*

Materyal ve Metot: *Çalışmamızda, 24 ay boyunca ≥18 ve <65 yaş arasındaki tüm olguların SIE MRG'leri retrospektif olarak değerlendirildi. Uluslararası Spondiloartrit Değerlendirmesi Derneği (ASAS) kriterlerine göre olguların verileri, görüntüleme sırasındaki yaşı, cinsiyeti, aktif ve kronik sakroiliit varlığı açısından analiz edildi. Tüm görüntüler Lumbosakral transizyonel vertebra (LSTV) varlığı ve major sakroiliak eklem varyasyonları açısından Castellvi sınıflandırma sistemi ile literatürde belirtilen kriterlere göre kategorize edilerek bu varyasyonlara eşlik eden yapısal ve ödematöz değişiklikler kaydedildi.*

Bulgular: *Çalışmaya dahil edilen 1020 MRG'nin 323'ünde SİE varyasyonları tespit edildi. SİE'lerin anatomik varyasyonlarının sıklık sırası şu şekildedir: 1) LSTV (114 hasta, %12,2), 2) Aksesuar sakroiliak eklem (80 hasta, %7,8), 3) İliyosakral kompleks (66 hasta, %6,4), 4) Sakral defekt (61 hasta, %5,9) ve 5) İzole sinostoz (2 hasta, %0,2). Ayrıca LSTV ve aksesuar SİE varyasyonuna, yapısal ve ödematöz bulgular sıklıkla eşlik ediyordu.*

Sonuç: *Bel ağrısı şikayeti ile başvuran ve SİE MRG planlanan özellikle kadın hastalarda, lumbosakral transizyonel vertebra ve sakroiliak eklem anatomik varyasyonları sıklıkla karşımıza çıkmaktadır. Ayrıca bu varyasyonlar, sakroiliiti taklit eden dejeneratif ve ödematöz sinyal değişikliklerine de yol açabileceğinden her zaman göz önünde bulundurulmalıdır.*

Anahtar kelimeler: *manyetik rezonans görüntüleme; sakroiliak eklem; anatomi; bel ağrısı*

Introduction

Spondyloarthritis (SpA) refers to a group of chronic inflammatory rheumatic diseases characterized by enthesitis and arthritis that commonly affect the axial skeleton[1–3]. Sacroiliac joint (SIJ) involvement in imaging (sacroiliitis) is part of the diagnostic algorithm for axial SpA, and it has been a crucial criterion according to the Assessment of Spondyloarthritis International Society (ASAS) classification since 2009[4]. Therefore, the SIJ's magnetic resonance

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imaging (MRI) has become the preferred imaging method because it reveals active inflammatory lesions in the early period before radiographic findings begin.

Although MRI is increasingly used to diagnose inflammatory back pain such as SpA and nonspecific low back pain (LBP), there are some uncertainties regarding the diagnostic value of degenerative and SpA-related MRI findings[5,6]. Therefore, more research is needed to expand the knowledge of pathoanatomical changes seen in MRI and to increase diagnostic accuracy in LBP.

However, in clinical practice, anatomical variations involving the ligamentous and cartilaginous parts of the SIJ make it challenging to evaluate. In SIJ MRI, findings such as bone marrow edema (BME) and sclerosis, which are signs of sacroiliitis, are also encountered in normal anatomical variations and degenerative processes. These variations and associated changes have previously been identified in some CT and MRI studies[7–11]. However, we believe they have not yet been studied in MRI with a large patient population.

Therefore, the primary purpose of this study is to investigate the frequency of normal anatomical variations and to reveal their importance by distinguishing the findings that mimic sacroiliitis in patients referred to MRI for LBP.

Materials and Methods

All consecutive MRI examinations of the SIJ patients aged 18–65 years performed due to LBP in our institution, a tertiary medical center, were evaluated between January 2018 and December 2019. One thousand three hundred and seventy (1370) consecutive MRI examinations were performed during the study period. Among those, we excluded patients with poor image quality and a history of metastasis, bone tumor, septic arthritis, or surgery. We also excluded patients whose information (such as age, gender, and final diagnosis before or after the MRI examination) could not be accessed. Consequently, 1020 patients (mean age 40.51±11.94, range 18–65) were enrolled in the study. There were 735 women (72.1%) and 285 men (27.9%).

Our study used classical sequences – paracoronal T1-weighted (T1W), short tau inversion recovery (STIR) images, and axial STIR images – for the SIJ scanning protocol. After intravenous gadolinium (Gd) contrast administration, the examination with contrast-enhanced (CE), fat-saturated axial, and paracoronal T1W sequences is completed. Examinations were conducted with the patient in the supine position using 1.5T or 3T magnets from manufacturers that use high-resolution body phased-array coil.

An experienced musculoskeletal radiologist reviewed all images. The images were assessed for the presence of structural and active sacroiliitis findings befitting the ASAS definition[4]. The morphologic features of sacroiliitis were assessed on axial STIR images and T1-weighted, fat-saturated images after administration of contrast material. At least two different locations of the SIJ of a characteristic BME must be identified to diagnose axial SpA. In the case of unilocular BME, this finding had to be present in at least two consecutive slices to meet the diagnostic criteria for axial SpA.

Major SIJ variations evaluated in addition to sacroiliitis according to the criteria described in the literature[12] are as follows:

- Accessory Sacroiliac Joint: A false joint between the sacral and iliac components, usually located at the S2 level in the dorsal part of the true synovial.
- Iliosacral Complex: An iliac protrusion placed in a complementary sacral recess in the posterolateral portion of the SIJ from the first sacral foramen level to the second sacral foramen.
- Sacral Defect: A round sacral defect in the posterior part of the sacrum unrelated to the presence of the opposite iliac defect in the axial plane.
- Transitional Vertebra: LSTV evaluation was based on the iliolumbar ligament, and the ligament-adherent vertebra was considered L5. Patients with and without dysplasia in the transverse process were classified according to the Castellvi radiographic classification system[13].

Laterality (unilateral or bilateral), associated structural and edematous changes in the bony surfaces, and the accompanying vascular structures to these variations were evaluated when one of the previous variations was observed.

The study data were evaluated using SPSS for Windows 15.0 software (SPSS Inc. Chicago, IL). The conformity of the variables to normal distribution was assessed visually (histogram and possibility graphs) and with analytical methods (Kolmogorov-Smirnov/Shapiro-Wilks tests). The Chi-square test (Fisher's Exact test) and Student's t-test were used for values conforming to the normal distribution. However, for values not conforming to the normal distribution, the Mann-Whitney U test $p<0.05$ was considered significant.

Results

Of 1020 patients, 88 had active sacroiliitis, 56 had chronic sacroiliitis, and 42 had signs of active and chronic sacroiliitis. We detected anatomical variation in 323 of 1020 patients who had SIJ MRI. The frequency order of anatomical variants of SIJs are as follows: 1) LSTV (114 patients, 12.2%), 2) Accessory sacroiliac joint (80 patients, 7.8%), 3) Iliosacral complex (66 patients, 6.4%) 4) Sacral defect (61 patients, 5.9%), and 5) Isolated synostosis (2 patients, 0.2%) (Table 1).

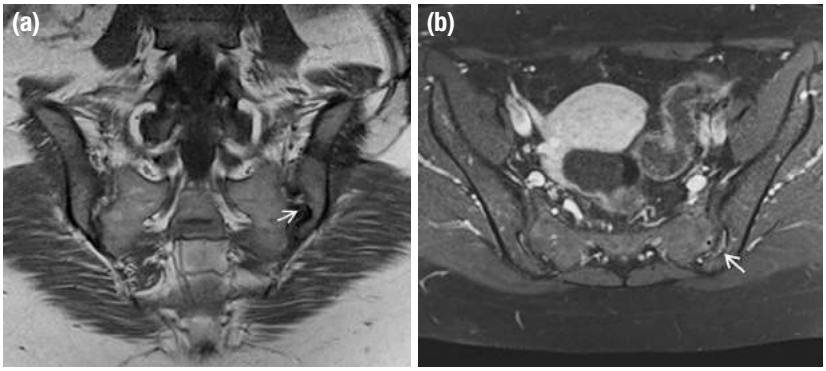

Figure 1. a, b. *Left accessory SIJ (arrows) was observed on paracoronal T1-weighted* ***(a)*** *and contrast-enhanced fat-saturated T1-weighted* ***(b)*** *axial images. Bone marrow edema at the sacral side and minimal sclerosis were seen in the left SIJ (asterisk).*

One hundred fourteen patients, 90 (78.9%) female, and 24 (21.0%) male, were classified as positive for LSTV. According to sacralisation classification, the most common anatomical variant was Castellvi Type Ia (3.8%), followed by Type Ib (2.5%). There were no statistically significant differences between men and women who had LSTV (p: 0.986). In addition, there was no significant correlation between the transitional vertebra and active or chronic sacroiliitis (p: 0.471).

Accessory SIJ was the second most common anatomical variant identified in 80 (12.2%) patients, 48 (60%) unilateral, and 32 (40%) bilateral. The joint is between the iliac and the sacral articular surfaces at the posterior portion of the SIJ, from the first to the second sacral foramen (Fig. 1). Accessory SIJ was also best detected in axial images, while LSTV and iliosacral complex were best seen in coronal images. Sacral defects were visualized in both axial and coronal images. Isolated synostosis was observed in only two of our cases, which were visualized in both axial and coronal images.

Thirty-two of 80 patients with accessory SIJ, 31 of 61 patients with sacral defects, and 37 of 66 patients with iliosacral complexes were bilateral. Bilateral status did not have a significant relationship with gender.

All the variations were more common in women but were not statistically significant compared with the male group. Only the incidence of sacral defects was significantly higher in males (p: 0.001) (Table 2).

Structural signal intensity changes – including subchondral sclerosis, subchondral cysts, osteophytes, and fatty deposition – were depicted in patients with LSTV and accessory SIJ. The most common structural signal intensities we detected were subchondral cysts and fatty deposits, as in 25 of 114 LSTV patients and 16 of 80 accessory SIJ patients.

We observed BME in 20 of 80 patients with accessory SIJ and 7 of 114 patients with LSTV (Fig. 2). However, compared with the association of sacroiliitis, there were no significant relationships (Table 3). Among the LSTV subgroups, the most common subgroup we observed with BME was Type 2a.

Table 1. *SIJ anatomical variations: prevalence, laterality, and associated changes*

	Variations (n: 323)	Laterality (n: 150)	BME (n: 27)	Structural changes (n: 41)	Prominent vascular (n: 52)
LSTV	114 (12.2%)	50 (33.3%)	7 (25.9%)	25 (60.1%)	0
Accesory SIJ	80 (7.8%)	32 (21.3%)	20 (74.1%)	16 (39.0%)	0
Iliosacral complex	66 (6.4%)	37 (24.6%)	0	0	20 (38.5%)
Sacral defect	61 (5.9%)	31 (20.6%)	0	0	32 (61.5%)
Synostosis	2 (0.2%)	0	0	0	0

Table 2. *Comparison of sacroiliac joint variations according to gender and age*

		Sex		Age	
		Female (%)	p[1]	Median (Q1-Q3)	p[2]
LSTV	+ (n: 114)	78.6%	0.096	40 (31–50)	0.373
	- (n: 906)	71.2%		43 (32–51)	
Accesory SIJ	+ (n: 80)	63.8%	0.092	40 (31–50)	0.493
	- (n: 940)	72.8%		38 (30–48)	
Iliosacral complex	+ (n: 66)	66.7%	0.192	40 (31–50)	0.648
	- (n: 954)	72.4%		39 (32–50)	
Sacral defect	+ (n: 61)	54.1%	**0.001**	37 (24–48)	0.093
	- (n: 952)	73.2%		41 (20–50)	

[1]Chi-Square analysis. [2]Mann-Whitney U analysis.

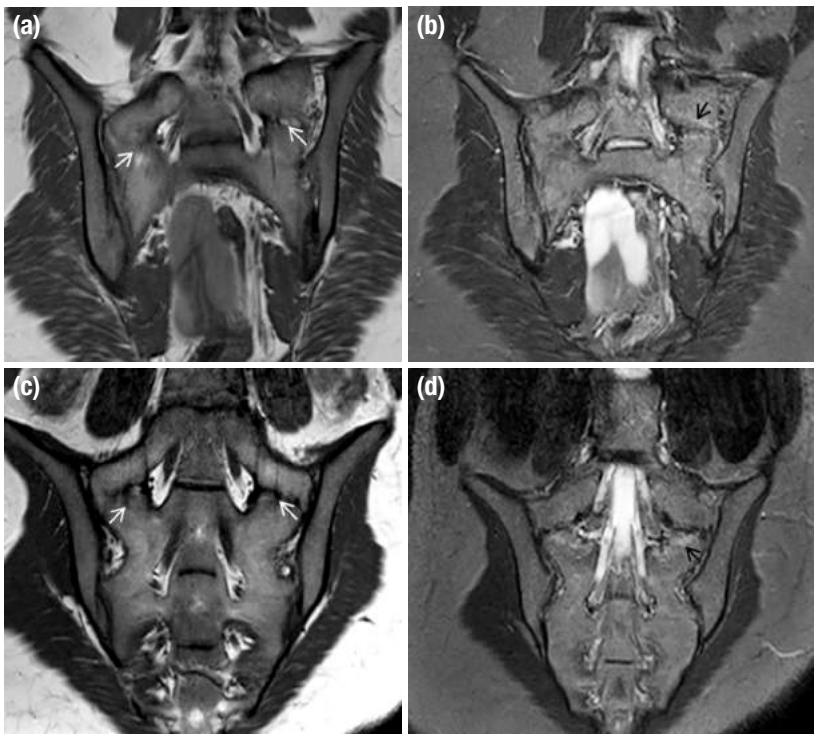

Figure 2. a–d. *Magnetic resonance imaging of SIJ demonstrates Castellvi type IV* ***(a)*** *and type IIB* ***(c)*** *sacralizations (white arrows) on paracoronal T1-weighted images. Contrast-enhanced fat-saturated T1-weighted images* ***(b, d)*** *demonstrate bone marrow edema at both sides of sacralization (black arrows).*

Accompanying prominent vascular structures occurred in 52 (41%) of the 127 patients with sacral defects and iliosacral complexes (Fig. 3).

Discussion

Since sacroiliitis is a hallmark of active SpA, according to the ASAS classification, MRI has become a crucial imaging biomarker of SpA for diagnosing and evaluating inflammation in patients with early disease[14]. However, it is important to know the common anatomical variations of the SIJ, as they can lead to diagnostic misinterpretation. Hence, we assessed the prevalence of anatomical variations on SIJ MRI in patients with LBP and highlighted their associations with sacroiliitis, gender, age, BME, and other structural changes.

Table 3. *Comparison of the BME according to the sacroiliitis and its correlation to LSTV and Accessory SIJ*

		BME +	BME -	Statistics	p
LSTV (+) (n: 114)	Sacroiliitis +	% 12.5 (n: 1)	% 16.0 (n: 17)	χ^2: 0.070	0.791
	Sacroiliitis -	% 87.5 (n: 7)	% 84.0 (n: 89)		
Accessory SIJ (+) (n: 80)	Sacroiliitis +	% 15.0 (n: 3)	% 16.7 (n: 10)	χ^2: 0.031	0.861
	Sacroiliitis -	% 85.0 (n: 10)	% 83.3 (n: 50)		

Column proportions are shown –Chi-square and Fisher's exact test used for analysis.

Only a few studies have reported the prevalence of MRI findings of anatomical variations on SIJ[11,15], but our study has the highest number of patients. We investigated anatomical variations in 323 patients among a total of 1020 aged 18–65 years.

LSTV was identified in 12.2% of our patients, and it was the most common variation. Castellvi et al.[13] reported a 30% prevalence in the LBP population and noted higher rates for Type IV, IIIB, and Type II. Their largest cohorts came from Type II (38.3%), whereas ours largely came from Type I (IA and IB) (57%). Reddy Ravikantha et al.[15] found the prevalence of LSTV to be 26.8% in their study with 500 patients, and their most common subgroup was Type IA (7.6%), as in our study.

Although LSTV was reported predominantly in men in the literature, there was no statistically significant difference between men and women who had LSTV in our study, as in Reddy Ravikantha et al.[15].

An MRI study conducted by Rafei et al.[11] provided the following results: "Accessory SIJ" in 17 (11%), "iliosacral

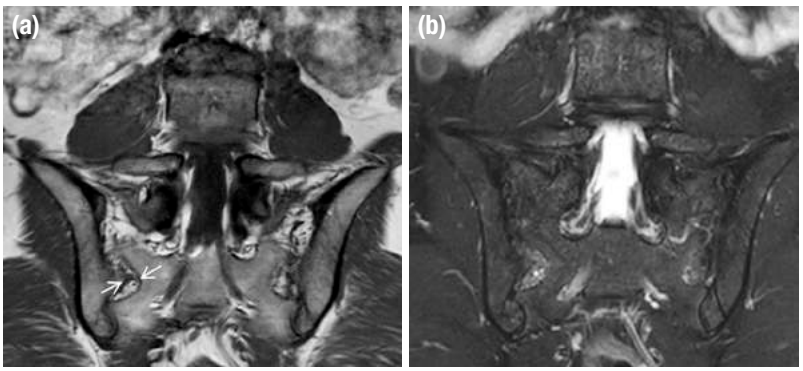

Figure 3. a, b. *Iliosacral complex on the right side on MRI. Paracoronal T1W image* ***(a)*** *showed protrusion of the ilium and concave depression of the sacrum on the opposite (arrows). This region's vascular structures (asterisks) may mimic enthesitis on T1W FS post-contrast axial images* ***(b)****.*

complex" in 18 (11%), "sacral defects" in 21 (13%), and "synostosis" in one (0.6%). In our study, however, accessory SIJ was the most common anatomical variation (7.8%, n=80), followed by the iliosacral complex (6.4% ; n=66), sacral defect (5.9%, n=61), and synostosis (0.2%, n=2).

Accessory SIJ is considered the most common variant, with a reported prevalence of 3.6–50%, and is also the most prone to degenerative changes and the most symptomatic[16–18]. One study reported that 64% (65/102) of the cases presenting with both LBP and degenerative changes were present[10].

In the current study among accessory SIJ patients, we found the prevalence of structural signal intensity changes, including subchondral cysts and fatty deposits, to be 20% and the prevalence of edematous changes as 25%. From experience, structural and degenerative changes resulting from anatomic variations in SIJ MRI can cause diagnostic misinterpretation. It is mostly associated with mechanical changes and should not be interpreted as sacroiliitis, especially in coronal images. Therefore, it will be useful to evaluate axial sequences for the diagnosis of accessory SIJ.

Although Eno et al.[19] found a relationship between SIJ degeneration and age in asymptomatic adults, no statistically significant difference was found between structural changes and age in our study.

In our reported 80 accessory SIJ patients, 20 (25%) cases demonstrated BME as a high signal on STIR images: four cases were bilateral, and 16 were unilateral. At the same time, 7 (6.1%) of 114 patients with LSTV were accompanied by BME. In light of the literature, the prevalence of LSTV in patients seeking care for LBP varies between 4.6% and 35.6% [20]. The prevalence of LSTV was 12.2% in our study, in which all patients had symptoms of LBP.

We did not find a statistically significant relationship between BME and the presence of sacroiliitis in either accessory SIJ and LSTV patients. LBP in the presence of an LSTV was initially noted by Mario Bertolotti in 1917 and termed "Bertolotti's Syndrome."

Quinlan et al.[21] found the prevalence of Bertolotti's syndrome to be 4.6% in the general population and 11.4% in patients under 30 years of age. Mahato et al.[22] also stated that the degeneration of abnormal articulation between the LSTV and the sacrum might lead to LBP. Although it has not been fully revealed yet, it is thought that LBP that develops due to this syndrome has various etiologies and arises from different locations.

In patients with LSTV, we also demonstrated that accompanying degenerative findings and BME can cause biomechanical alterations independent of sacroiliitis and associated with LBP. In our experience, we think the prevalence we detected may reflect the real situation encountered in routine clinical practice, as only symptomatic patients require SIJ MRI.

Iliosacral complex and semicircular defects, which are anatomical variants seen in the ligamentous part of the SIJ, were not associated with any degenerative changes in our study since they do not have facing bony surfaces. We found their prevalence similar to previous CT studies[8,10].

Prassopoulos et al.[10] reported that these anatomical variants were more common in women and were not associated with age or body mass index. Similarly, in our study, they were observed more frequently in women.

Since the transitional zone between the cartilaginous and ligamentous part of the sacroiliac joint is rich in vessels[12,23], it should be kept in mind that the evident vascular structures in this area, especially in coronal images, may mimic enthesitis. It should always be evaluated with axial images to avoid this potential pitfall.

We found only two synostoses partially involving SIJ in our study. As these variations mimic ankylosis, it is essential to demonstrate that the remaining parts of the bilateral joints are free of structural and edematous damage. Our findings were similar to those of the other two previous studies demonstrating synostosis[11,24].

Our study has some limitations. First, its retrospective design entails selection bias. However, the widespread use of MRI in our country and the ease of patients' access to health services at the university hospital level make our study group close to setting an example to determine the true prevalence of anatomical variations. Second, referring only symptomatic patients for whom the diagnosis was unavailable for SIJ MRI examination by clinicians may mean that asymptomatic variations and their definitive diagnosis were not included in this study. Thus, no definitive interpretation can be made about the true incidence of BME. The follow-up period of the patients in our study was not long enough; however, the purpose of our study was not to evaluate the true prevalence of sacroiliitis but to increase the awareness of radiologists of SIJ variations in daily practice. Finally, although the number of cases in this series is small, to our knowledge, this study is the most comprehensive published series of sacroiliac joint anatomical variations, focusing solely on MRI features.

SIJ variations have an MRI prevalence of approximately 31.6% in the target population. Based on our data, we conclude that LSTV and several anatomical SIJ variations are common in the LBP population, especially in females. These variations may be associated with degenerative and edematous signal intensity changes mimicking sacroiliitis. Therefore, radiologists should be aware of these anatomical variations when analyzing the SIJ MR images of a patient with low back pain.

Ethical Approval

This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and the local Institutional Review Board approved it.

Patients' Consent

As this study was retrospective, the patients' consent was waived.

Conflict of Interest

The author declared no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Association of Admission Troponin Levels with Hospitalization and Mortality in COVID-19 Patients

COVID-19 Hastalarında Başvuru Sırasında Ölçülen Troponin Değerlerinin Hastaneye Yatış ve Mortalite ile İlişkisi

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ABSTRACT

Aim: *This study aims to identify the association of cardiac Troponin T (cTnT) levels with hospitalization and in-hospital mortality in patients admitted to the emergency department (ED) and diagnosed with COVID-19.*

Material and Method: *Retrospectively, we scanned the data of adult patients presenting to the ED of a university hospital within 50 days of the first COVID-19 case admission (March 2020 – May 2020). The study group consisted of patients diagnosed with COVID-19 by reverse-transcriptase polymerase chain reaction, and had cTnT test. Demographic and laboratory data, thoracic computed tomography (CT) imaging findings, and length of hospital stay were also collected. The study outcomes were patients' hospitalization status and in-hospital mortality.*

Results: *Out of 36 patients, 9 (25%) were discharged, 20 (55.6%) remained in-patients in the ward, and 7 (19.4%) in the intensive care unit. When overall in-patients were compared to discharged patients, a significant difference was observed with regard to age [median (25% -75%)] [60 (45–69) to 28 (26–39.5) years, respectively; p=0.003)], thoracic CT score [6 (0–11) to 0 (0–0.5), respectively; p=0.005], admission cTnT values [5.99 (3.50–15.55) to 3 (3–3.28) ng/L; p=0.012]. The mortality rate among in-patients was 18.5%. In the multivariate cox regression model, none of these parameters significantly affected survival.*

Conclusion: *The cTnT values of COVID-19 patients are likely to be associated with hospitalization and mortality. Thoracic CT score was higher in patients admitted to the intensive care unit. However, neither cTnT values nor thoracic CT scores have a statistically significant effect on survival, even if their distributions are different between survived and non-survived groups.*

Key words: *COVID-19; computed tomography; emergency department; hospitalization; mortality; troponin*

ÖZET

Amaç: *Bu çalışmanın amacı acil servise (AS) başvuran ve COVID-19 tanısı koyulan hastalarda, kardiyak troponin T (cTnT) düzeylerinin hastaneye yatış ve hastane içi mortalite ile ilişkisini belirlemektir.*

Materyal ve Metot: *Çalışma 3. basamak sağlık hizmeti veren bir üniversite hastanesinin acil servisinde gerçekleştirilmiştir. Retrospektif özelliktedir. Çalışmaya Mart 2020-Mayıs 2020 tarihleri arasında ardışık 50 gündeki erişkin hastalar dahil edilmiştir. Çalışma grubu, ters transkriptaz polimeraz zincir reaksiyonu ile COVID-19 tanısı koyulan ve cTnT testi yapılan hastalardan oluşmaktadır. Hastaların demografik ve laboratuvar verileri, torasik bilgisayarlı tomografi (BT) görüntüleme bulguları, hastanede kalış süreleri not edilmiştir. Çalışma sonlanımı olarak hastaların hastaneye yatış durumu ve hastane içi mortalite bilgileri belirlenmiştir.*

Bulgular: *Çalışmaya alınan 36 hastanın 9'u (%25) taburcu edilmiş, 20'si (%55,6) servise, 7'si (%19,4) yoğun bakıma yatırılmıştır. Yatan hastalar ile taburcu edilen hastalar karşılaştırıldığında, yaş [medyan (%25–75)] [sırasıyla 60 (45–69) ila 28 (26–39,5) yıl; p=0,003)], torasik BT skoru [sırasıyla, 6 (0–11) ila 0 (0–0,5); p=0,005], başvuru cTnT değerleri [5,99 (3,50–15,55) ila 3 (3–3,28) ng/L; p=0,012] olarak bulunmuştur. Yatan hastalarda ölüm oranı %18,5 idi. Çok değişkenli cox regresyon modelinde bu parametrelerin hiçbiri hayatta kalma üzerinde anlamlı bir etkiye sahip değildir.*

Sonuç: *COVID-19 hastalarının cTnT değerlerinin hastaneye yatış ve mortalite ile ilişkili olması muhtemeldir. Yoğun bakım ünitesine yatırılan hastalarda toraks BT skoru daha yüksektir. Ancak cTnT değeri ve torasik BT skorları hayatta kalan ve ölümle sonuçlanan gruplar arasında farklı izlenmiş olsalar bile sağ kalım üzerinde istatistiksel olarak anlamlı bir etkiye sahip değildir.*

Anahtar kelimeler: *acil servis; toraks bilgisayarlı tomografisi; COVID-19; hastaneye yatış; mortalite; troponin*

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Introduction

Troponin is a protein involved in the striated muscle contraction complex. Blood levels of cardiac troponins (cTnI and cTnT) may be elevated after direct damage to the heart muscle, including myocardial infarction, myocarditis, and cardiac contusions, or due to various other reasons such as pneumonia, cerebral pathologies, heart failure, sepsis, pulmonary embolism, burns, and cardiotoxic drugs[1]. Although the reason for elevation in each clinical case cannot be identified separately, changes in cardiac troponins are associated with inflammatory markers and age[2]. More importantly, elevated cardiac troponin is responsible for all-cause mortality during the in-hospital stay and in the long term[1,3].

As a separate issue, COVID-19 is a disease induced by the virus called SARS-CoV-2, which targets both the respiratory tract and other systems in the body[4]. Its major clinical manifestations are fever, cough, muscle aches, weakness, diarrhea, and in more severe cases, shortness of breath and chest pain[4]. While its diagnosis is mainly established by nucleic acid amplification tests and serological tests, other laboratory tests (complete blood count, biochemical tests) or thoracic computed tomography (CT) are used to support the diagnosis, predict the prognosis and exclude differential diagnoses[5]. So far, the highly contagious SARS-CoV-2 virus has infected many people worldwide, causing millions of deaths.

Within this framework, this study aims to assess the demographic characteristics and hospitalization and mortality rates of patients admitted to the emergency department (ED), diagnosed with COVID-19, and subjected to the cTnT test. Moreover, we would like to set a value to cTnT or thoracic CT scores in hospitalized or deceased COVID-19 patients, if any.

Material and Method

Study Design and Population

Our tertiary-level healthcare facility receives approximately 120.000 admissions annually. We retrospectively scanned the data of adult patients (18 years and older) presenting to our ED within 50 days from the admission of the first COVID-19 case (March 2020-May 2020), receiving the diagnosis of COVID-19 through reverse-transcriptase polymerase-chain-reaction (RT-PCR), and undergoing a cTnT test. On the other hand, the data on pregnant women and patients referred to our hospital after the initiation of treatment from an external clinical center were excluded. Treatment of the patients was performed by current guidelines, yet these data were not included in the study[6].

Ethical Approval

We obtained ethical approval from the Medical Ethics Committee of Pamukkale University with an approval number of 23.06.2020/2 and followed the Helsinki Declaration guidelines over the study. Since this is a retrospective study, no patient consent was requested, and descriptive patient information was not reported in this article.

Data Collection

Our patients' admission complaints, demographic data, concomitant diseases and habits, laboratory data (complete blood count, blood biochemistry, D-dimer and cTnT values), and thoracic CT findings[7,8] in the last six days were noted in the study form. The laboratory and diagnostic imaging tests were performed in light of current diagnosis-treatment guideline recommendations[6]. The cTnT values were recorded as the baseline value measured at admission to ED (baseline cTnT) and the maximum value (max. cTnT) measured during a hospital stay. The reference range of the cTnT value in our healthcare facility is 0–14 ng/L.

A Board-certified radiologist with more than ten years of professional experience interpreted thoracic CT findings and scored COVID-19 lung involvement[8]. This scoring system is based on lung involvement in COVID-19 patients. Involvement of each of the five lobes is calculated as a percentage. 25% of each involved lobe is equal to 1 point. Total score ranges from 0 to 20, 0 meaning no lung involvement, and 20 with all five lobes involvement[8]. The association of the scoring with patient mortality was also investigated.

Furthermore, we noted the presence and number of comorbid diseases (i. e., malignancy, diabetes mellitus (DM), hypertension (HT), coronary artery disease, rheumatological diseases, lung diseases, chronic renal failure, chronic liver failure).

The primary outcomes were accepted as patients' discharge from ED, hospitalization, or admission to the intensive care unit (ICU). If the patients were admitted to ICU at any time during their hospital stay, they were included in the ICU in-patient group. The secondary outcomes were the length of hospital stay and in-hospital mortality.

Statistical Analysis

All the statistical analyses of the obtained clinical and demographic data were performed using Statistical Package for the Social Sciences (SPSS) v. 25 (IBM Corp., Armonk, NY, USA). Continuous variables were provided as mean ± standard deviation; median (minimum-maximum values), median (IQR), and categorical variables as numbers and percentages. Shapiro Wilk

test was used for the determination of normal distribution. For independent groups comparisons, we used the independent samples t-test and One Way Analysis of Variance (post hoc: Tukey method) when parametric test assumptions were provided, Mann Whitney U test and Kruskal Wallis Variance Analysis (post hoc: Mann Whitney U test with Bonferroni Correction) were used when parametric test assumptions were not provided. In addition, a Spearman or Pearson correlation analysis was performed to investigate the relationships between continuous variables, whereas the differences between categorical variables were analyzed using a Chi-square test. We used univariate and multiple cox regression models to determine the factors affecting survival. A p-value of <0.05 was set as the limit for statistical significance.

Results

Table 1 provides an overview of the descriptive characteristics and admission reasons of 36 patients (23 males, 13 females, mean age 51.89±20.32; median age 52.5 years; age range 18–99 years). Twenty-six (72%) were under 65 years old, while 10 (28%) were 65.

Out of 30 patients whose medical history could be extracted, 13 (43.3%) had no concomitant disease, and 10 (33.3%) were afflicted with two or more comorbidities (Table 1). Of 31 patients whose smoking status was recorded in the system (29%), 9 were active smokers. Seven were hospitalized (2 in ICU, 5 in the ward), and two died in ICU.

Whereas nine patients (25%) were discharged from the ED and followed up as outpatients via telephone, 20 (55.6%) remained in-patients in the ward and 7 (19.4%) in ICU. The mortality rate among the in-patients was 18.5%, and a considerable proportion of mortality (80%) was observed in the patients hospitalized directly from the ED to the ICU. The average hospital stay of all the patients was 10.2±7.9 days (2–42 days).

When in-patients were compared to patients discharged from the ED, a significant difference was observed in relation to age [median (IQR)] [(60 (45–69) to 28 (26–39.5) years, respectively; p=0.003)], thoracic CT score [6 (0–11) to 0 (0–0.5), respectively; p=0.005)], the highest cTnT values on admission and hospitalization [5.99 (3.50–15.55) to 3 (3–3.28) ng/L; p=0.012 and 7.04 (3.5–54.75 to 3 (3–8.71) ng/L; p=0.019, respectively], blood lymphocyte count (1.41±0.69 to 2.08±1.03; p=0.037), glucose [118 (103.75–160.25) to 93 (82–102.5) mg/dL, respectively; p=0.001], D-dimer values [350 (106.25–1113.00) to 41 (13.25–86.75) ng/mL; p=0.010], CRP levels [17.97 mg/L (3.06–86.22) to 1.16 (0.25–15.97); p=0.013], and aspartate aminotransferase (AST) [21.5 (17.25–33.5) to 17 (13–19.5) IU/L, respectively; p=0.018)]. Table 2 lists the results from comparing the detailed subgroups (patients discharged from ED, ward-patients, and ICU patients).

The mean cTnT values of the patients were [median (IQR)] 4.26 (3.00–11.81) ng/L, and 22% were above the accepted threshold value. Maximum cTnT values at baseline and during hospitalization were observed to correlate with age (r=0.845; r=0.739, respectively; p=0.000 for both). The patients with admission cTnT values above the 99th percentile, so interpreted as "positive cTnT," turned out to be older (75.25±13.28 years old vs. 45.21±16.78 years old; p=0.000). In addition, these patients had higher neutrophil counts [median (IQR)] [8.78 (4.9–11.72) vs 4.55 (3.28–6.43) K/uL; p=0.022] and D-dimer values [1095 (665.5–1786.0) vs. 66 (24.5–231.5) ng/mL; p=0.004]. By contrast, they had lower lymphocyte counts (0.96±0.70 vs 1.77±0.78; p=0.013) and hemoglobin values [11.60 (10.12–12.70) vs. 14.30 (13.50–15.90) md/dL; p=0.001].

Some parameters, including age, baseline cTnT, lymphocyte, NLR, D-dimer, CRP, hematocrit, blood urea nitrogen, AST, and maximum cTnT, differed significantly in the cases resulting in mortality (Table 3).

Thoracic CT results of 13 (36.1%) individuals were reported as normal, while peripherally located ground-glass appearance was observed in 19 (54.3%) patients. Besides, other less frequent findings, such as central location, consolidation, septal thickening, pleural

Table 1. *Demographic characteristics of the patients and their admission complaints*

Gender, n (%)		
	Male	23 (64)
	Female	13 (36)
Age, years (mean ± standard deviation)		51.89±20.32
Admission complaints, n (%)		
	Fever	10 (28)
	Malaise	11 (30)
	Cough	11 (30)
	Shortness of breath	7 (19)
	Sore throat	5 (14)
	Others	7 (19)
Concomitant diseases, n (%)		
	Diabetes Mellitus	9 (30)
	Hypertension	9 (30)
	Coronary artery disease	7 (23)
	Chronic renal failure	2 (6)
	Rheumatological diseases	2 (6)
	Others	8 (24)
Habits, n/31 (%)		
	Smoking	9/31 (29)

n, number of patients.

Table 2. *Patients' age, laboratory, and imaging findings among three subgroups (patients discharged from the ED, hospitalized on regular wards, and admitted to the ICU)*

		Discharged patients	Patients hospitalized on regular wards	ICU admissions	p
Female/Male, n		3/6	8/12	2/5	0.844 †
Age, years	mean ± SD	37.22±24.06 [a]	52.05±16.09 [ab]	70.29±9.94 [b]	**0.002** **
	median (IQR)	28 (26–39.5) [a]	52.5 (40.75–63.75) [ab]	69 (63–77) [b]	
Concomitant diseases, (absent/present), %		87.5/12.5	40/60 [a]	0/100 [a]	**0.003** †
Number of concomitant diseases, (none/1/more than 1), %		87.5/12.5/0	40/26.7/33.3 [a]	0/28.6/71.4 [a]	**0.002** †
Diabetes mellitus, (absent/present), %		100/0 [a]	73.3/26.7 [ab]	28.6/71.4 [b]	**0.004** †
Hypertension, (absent/present), %		100/0 [a]	73.3/26.7 [ab]	28.6/71.4 [b]	**0.004** †
Coronary artery disease, (absent/present), %		87.5/12.5	80/20	57.1/42.9	0.369 †
Admission cTnT, ng/L	mean ± SD	10.73±22.98 [a]	7.29±7.47 [a]	31.11±25.34	**0.002** **
	median (IQR)	3 (3–3.29) [a]	4.26 (3.03–7.55) [a]	19.46 (7.31–59.9)	
Max. cTnT, ng/L	mean ± SD	11.93±22.78 [a]	13.51±19.49 [a]	205.75±276.93	**0.001** **
	median (IQR)	3 (3–8.72) [a]	4.72 (3.09–11.49) [a]	107.7 (19.46–219)	
Thoracic CT score	mean ± SD	1±2.64 [a]	5.1±4.86 [ab]	9.86±6.31 [b]	**0.006** **
	median (IQR)	0 (0–0.5) [a]	3.5 (0–10.5) [ab]	11 (6–13) [b]	
Glucose, mg/dL	mean ± SD	98.44±22.73	132.74±47.23 [a]	166.43±67.92 [a]	**0.003** **
	median (IQR)	93 (82–102.5)	114 (103–155) [a]	141 (109–211) [a]	
Lymphocyte count, K/uL	mean ± SD	2.08±1.03 [a]	1.58±0.63 [ab]	0.96±0.70 [b]	**0.014** **
	median (IQR)	2.24 (1.62–2.36) [a]	1.53 (1.02–1.92) [ab]	0.79 (0.5–0.91) [b]	
NLR	mean ± SD	9.26±19.72	5.17±4.89	8.69±7.00	0.118 **
	median (IQR)	1.9 (1.62–5.85)	2.73 (1.97–5.8)	5.79 (4.13–13.51)	
D-dimer, ng/mL	mean ± SD	52.00±50.33 [a]	488.13±633.08 [ab]	1225.75±915.46 [b]	**0.013** **
	median (IQR)	41 (13.25–86.75) [a]	277.5 (60.75–845.25) [ab]	1107 (450.75–2119.5) [b]	
CRP, mg/L	mean ± SD	8.55±14.42 [a]	37.34±61.87 [ab]	76.40±51.47 [b]	**0.006** **
	median (IQR)	1.16 (0.25–15.98) [a]	6.91 (2.15–54.84) [ab]	86.5 (20.21–124.42) [b]	
Hematocrit, %	mean ± SD	43.36±3.94 [a]	41.39±5.18 [a]	35.37±5.14	**0.008** *
	median (min-max)	43.2 (38.2–49.1) [a]	41.1 (29–49.4) [a]	36 (29.4–41.2)	
Blood urea nitrogen, mg/dL	mean ± SD	12.44±5.45 [a]	13.53±8.00 [a]	19.71±5.15	**0.015** **
	median (IQR)	12 (9.5–13) [a]	11 (9–15) [a]	19 (14–25)	
Creatinine, mg/dL	mean ± SD	0.86±0.20	0.92±0.44	1.12±0.67	0.887 **
	median (IQR)	0.93 (0.67–1.02)	0.83 (0.67–1)	0.93 (0.53–1.86)	
Aspartate aminotransferase, IU/L	mean ± SD	16.56±3.74 [a]	21.84±8.14 [a]	35.86±15.10	**0.001** *
	median (min-max)	17 (12–23) [a]	21 (10–42) [a]	38 (15–61)	
Length of stay, days	mean ± SD	0.33±0.21 [a]	8.1±2.42 [b]	16.14±14.20 [c]	0.0001 *
	median (min-max)	0.36 (0.08–0.67) [a]	7.5 (5–13) [b]	18 (2–42) [c]	

CRP, c-reactive protein; cTnT, cardiac troponin T; ICU, intensive care unit; IQR, interquartile range; Max cTnT, maximum cTnT value measured during hospital stay; Min, minimum; NLR, neutrophil lymphocyte ratio; SD, Standard deviation; Thoracic CT score, thoracic computed tomography score. *, One Way Analysis of Variance; **, Kruskal Wallis Variance Analysis; †, Chi-Square Analysis. The difference between groups that do not carry the same letter in each column is important (p<0.05).

effusion, and air bronchograms, were detected in the tomography imaging of 4 (11.4%) individuals. When CT scoring was used to identify the prevalence of lung involvement[8], the median value corresponded to 3.5 (min: 0, max: 20).

Thoracic CT score was not associated with being under 65 years old or older [median (IQR)] [1.5 (0–9.5) to 7.5 (0–11); p=0.350] or baseline and maximum cTnT values [3.28 (3–5.49) to 15.62 (5.99–72.02) ng/L, p=0.000; 3.71 (3–8.12) to 72.19 (11.38–122.67) ng/L, p=0.000, respectively]. However, a significant increase was observed in CT scores [0 (0–0.5) vs. 6 (0–11); p=0.005] when discharged patients were compared with a total of the ward and ICU patients, respectively. Although CT scores seemed to vary in the cases ending up with mortality [2 (0–9) to 11 (3.5–16.5); p=0.082], this did not yield a significant difference (Table 3).

The Cox regression model created to examine the factors that affect survival showed that age, presence of diabetes mellitus and HT, thoracic CT score, lymphocyte count, and AST values had a statistically significant effect on survival in univariate analyzes. While increasing age, presence of DM, presence of HT, increase in thoracic CT score and increase in AST value have a significant lowering effect on survival probability, an increase in lymphocyte count significantly increases the probability of survival. In the

Table 3. *Age, laboratory, and imaging findings in survivors and non-survivors*

		Non-survivors	Survivors	p
Female/Male, n		2/3	11/20	
Age, years	mean ± SD	66±7.74	49.61±20.86	**0.005** *
	median (min-max)	65 (56–77)	49 (18–99)	
Concomitant diseases, (absent/present), %		0/100	52/48	0.052 **
Number of concomitant diseases, (none/1/more than 1), %		0/40/60	52/20/28	**0.04** **
Diabetes mellitus, (absent/present), %		20/80	80/20	**0.019** **
Hypertension, (absent/present)%		40/60	76/24	0.143 **
Coronary artery disease, (absent/present), %		60/40	80/20	0.565 **
Admission cTnT, ng/L	mean ± SD	29.07±25.79	10.15±16.26	**0.012** †
	median (IQR)	19.46 (6.65–56.31)	3.93 (3–7.87)	
Max. cTnT, ng/L	mean ± SD	123.35±75.09	38.75±144.64	**0.001** †
	median (IQR)	107.7 (61.23–193.3)	4.49 (3–12.7)	
Thoracic CT score	mean ± SD	10.2±7.39	4.16±4.75	0.082 †
	median (IQR)	11 (3.5–16.5)	2 (0–9)	
Glucose, mg/dL	mean ± SD	169.0±74.77	124.27±45.26	0.077 †
	median (IQR)	141 (119–233)	108 (98.25–151)	
Lymphocyte count, K/uL	mean ± SD	0.69±0.21	1.73±0.8	**0.007** *
	median (min-max)	0.71 (0.45–0.91)	1.78 (0.14–4.03)	
NLR	mean ± SD	10.99±7.03	6.24±11.25	**0.014** †
	median (IQR)	7.68 (5.78–17.88)	2.5 (1.83–5.76)	
D-dimer, ng/mL	mean ± SD	1555.67±777.2	296.87±498.16	**0.01** †
	median (IQR)	1119 (1095–2453)	68 (32–328)	
CRP, mg/L	mean ± SD	85.62±55.26	29.77±52.2	**0.019**†
	median (IQR)	115.56 (26.4–129.89)	5.22 (1–29.69)	
Hematocrit, %	mean ± SD	35.36±5.66	41.58±5.06	**0.017** *
	median (min-max)	36 (29.4–41.2)	41.2 (29–49.4)	
Blood urea nitrogen, mg/dL	mean ± SD	18.8±5.63	13.77±7.33	**0.029** †
	median (IQR)	17 (14–24.5)	12 (9–15.5)	
Creatinine, mg/dL	mean ± SD	0.9±0.68	0.95±0.42	0.268 †
	median (IQR)	0.56 (0.48–1.51)	0.86 (0.7–1.02)	
Aspartate aminotransferase, IU/L	mean ± SD	40.6±14.25	20.4±7.58	**0.002** †
	median (IQR)	40 (29.5–52)	19 (13.75–25.25)	
Length of stay, days	mean ± SD	10.6±9.81	7.26±7.92	0.448 †
	median (IQR)	7 (2–21)	7 (0.53–10)	

CRP, c-reactive protein; cTnT, cardiac troponin T; IQR, interquartile range; Max. cTnT, maximum cTnT value measured during hospital stay; Min, minimum; NLR, neutrophil lymphocyte ratio; SD, standard deviation; Thoracic CT score, thoracic computed tomography score; *, Independent samples t-test; **, Chi-Square test; †, Mann-Whitney U test.

multivariate model established with these variables, none of them had a significant effect on survival (Table 4).

Discussion

COVID-19 might be a major driver of widespread inflammation in the body. Multiple lines of evidence suggest that marked changes were observed in the levels of many inflammatory markers, such as C-reactive protein, procalcitonin, IL-6, ferritin, fibrinogen, TNF-α, and IFN-γ in COVID-19 infection[9]. In a clinical trial on 172 adult patients hospitalized in ICU for non-cardiac reasons, troponin was closely linked to sepsis and IL-6 in 42% of patients with increased plasma cTnT at least once during follow-up[2]. Besides, troponin may elevate in the course of many serious diseases, most notably cerebrovascular events, other than sepsis[1,2,10]. Though the exact cause of this elevation remains a mystery, it is assumed that ventricular strain might trigger inflammation and the activation of the coagulation cascade, also related to inflammation[2,11]. Although acute myocardial infarction was not an exclusion criterion in our study, none of our patients received this diagnosis during the in-hospital or telephone follow-up of initially discharged patients from the ED. Moreover, the follow-up documents revealed that only one patient manifested signs of heart failure. These values of all other patients with increased plasma cTnT might be

Table 4. *Cox Regression Analysis of predictors possibly related to survival*

	Univariate					Multiple				
	Wald	p	HR	95.0% CI for HR		Wald	p	HR	95.0% CI for HR	
				Lower	Upper				Lower	Upper
Gender	1.504	0.22	1.658	0.739	3.721					
Age	**11.748**	**0.001**	**0.959**	**0.937**	**0.982**	1.535	0.215	0.978	0.945	1.013
Diabetes Mellitus	**5.15**	**0.023**	**0.313**	**0.115**	**0.854**	1.181	0.277	0.49	0.135	1.774
Hypertension	**4.218**	**0.04**	**0.348**	**0.127**	**0.953**	0.285	0.593	0.713	0.205	2.472
Coronary artery disease	2.478	0.115	0.419	0.142	1.238					
Thoracic CT score	**5.478**	**0.019**	**0.91**	**0.841**	**0.985**	1.096	0.295	0.931	0.814	1.064
Admission cTnT, ng/L	2.571	0.109	0.979	0.954	1.005					
Max. cTnT, ng/L	1.806	0.179	0.997	0.993	1.001					
Glucose, mg/dL	1.119	0.29	0.995	0.987	1.004					
Lymphocyte count, K/uL	**4.727**	**0.03**	**1.617**	**1.048**	**2.494**	2.807	0.094	2.095	0.882	4.977
NLR	0.013	0.911	1.003	0.955	1.052					
D-dimer, ng/mL	2.543	0.111	0.999	0.998	1					
CRP	3.246	0.072	0.991	0.982	1.001					
Hematocrit, %	3.548	0.06	1.07	0.997	1.148					
Blood urea nitrogen, mg/dL	1.419	0.234	0.965	0.911	1.023					
Creatinine, mg/dL	0.78	0.377	0.675	0.282	1.616					
Aspartate aminotransferase, IU/L	**9.188**	**0.002**	**0.932**	**0.891**	**0.975**	1.175	0.278	0.965	0.905	1.029

CI, confidence interval; CRP, c-reactive protein; cTnT, cardiac troponin T; ICU, intensive care unit; HR, hazard ratio; Max. cTnT, maximum cTnT value measured during hospital stay; NLR, neutrophil lymphocyte ratio; Thoracic CT score, thoracic computed tomography score. Cox Regression Analysis.

induced by possible inflammation and subsequent processes, perhaps by microthrombi. Similar results would presumably have been achieved if a diagnostic autopsy of our patients had been performed.

Our results also indicate that cTnT values at baseline and during follow-up tended to increase with age. Comorbidities may also be the culprit of troponin elevation in our patients, as these conditions may multiply with advancing age. In any case, the higher mortality rate among patients with increased cTnT concentrations suggests that this parameter can act not only as a cardiac marker but also as a prognostic marker for COVID-19.

Clinical trials published worldwide post-COVID-19 period have revealed that this disease proves more fatal, especially in geriatric patients[4,12]. In our case, both the disease's mortality rate and the ICU admission rate turned out to be higher in elderly patients. With further comorbid conditions, this situation is not unique to COVID-19 infection but may also be associated with decreased immunity in geriatric patients.

In a clinical study performed on 257,947 patients in the UK over seven years, the rate of troponin measurement and positive troponin values in patients admitted to ED tended to increase with age[3]. In addition, the study also provides further evidence for the association between positive troponin values and mortality across all age groups, especially in young people[3]. The interplay between positive troponin values and increased all-cause mortality within the hospital and in the long term in many diseases is also well-documented[1,3,11].

The elimination of cTnT is known to occur through the renal system, yet previous research has yielded conflicting information on plasma cTnT levels in patients with renal failure. A clinical report on the significant renal role in eliminating cTnT suggests that cTnT concentration increased in both plasma and urine in the pre-dialysis blood samples of all end-stage renal disease patients without heart disease[13]. In a six-year follow-up study on over-65-year-olds suffering from compensated chronic renal failure with an eGFR <20 mL/min/1.73 m^2, the basal values of troponin tended to increase each year, and its association with GFR was independent of each other[14]. In our study, creatinine value remained above 2 mg/dL (GFR ≥29 mL/min/1.73 m^2) in only two patients, and none received chronic hemodialysis treatment. We presume that the baseline cTnT values were not significantly affected by renal insufficiency because our patients were younger than their counterparts in the studies above and because of the number of patients with chronic renal failure.

In a recent study comparing patients who tested positive and negative for COVID-19 as a result of RT-PCR, positive patients were reported to have higher

neutrophil, CRP, AST, and urea values and lower lymphocyte count[15]. Our research population consisted of cases with only positive RT-PCR results. Similar parameters showed significant changes in hospitalization and mortality in our patient cohort.

A meta-analysis reports that COVID-19 disrupts hemoglobin in red blood cells (RBC), significantly reducing hemoglobin values in critically ill patients[16]. Fluid therapy and RBC transfusion therapy administered to improve tissue perfusion in sepsis has fallen out of favor in recent guidelines. However, some case reports on a limited number of patients with hemoglobinopathy or gastrointestinal-induced blood loss provide clinical evidence that blood transfusion can yield substantial improvement in vital parameters and prognosis of patients[17,18]. Besides, thrombotic microangiopathy events observed in COVID-19 patients can induce consumption coagulopathy and bleeding[9]. Early blood product transfusion may also be considered among the treatment options for these patients in whom early anticoagulants were initiated for treatment or protection from thromboembolism (prophylaxis). In another recent research, 184 ICU patients diagnosed with COVID-19 pneumonia were reported to develop high venous and arterial thromboembolic complications despite prophylaxis, and the researchers recommended increasing prophylactic dosage[19]. In that regard, our study supports these data. Hematocrit values of our ICU patients and non-survivors were lower than their counterparts. We also observed changes in fibrin-degradation products' (such as D-dimer) values that were checked on admission.

A study with a cohort of 1099 patients with COVID-19 identified cough as the most prevalent complaint (67.8%), and almost one quarter (23.8%) of these patients had one or more accompanying diseases. Their hospital stay was 12 days (IQR 10–14), which increased to 14.5 days (IQR 11–19) in ICU patients, those with endotracheal intubation or non-survivors[4]. In our investigation, the length of stay in ICU (18 (IQR 2–42) days) was longer than that in the ward, and this period, although not significant, (7 (IQR 0–10) days) tended to be shorter in non-survivors than in the survivors. Our patients admitted to the ICU have more co-morbidities, advanced age, and worse lung imaging findings. This may have caused a longer treatment. Deaths occurred in patients hospitalized in the ICU. We assume that a higher incidence of death in the acute period may be due to the late admission of these patients to the hospital. In our study, the symptom onset time was not questioned. These patients' mortality causes were determined as ARDS, mods, and septic shock, but no definite cause of arrest was identified. Since it is known that COVID-19 can cause hypercoagulability[9,11,19], these patients may have died before being diagnosed.

This information suggests that mortality occurs earlier, and patients who survive early complications have a higher tendency to recover in the following days.

Thoracic CT images display pathological findings at a sensitivity of 97% in cases with a confirmed diagnosis by RT-PCR[1]. These are bilaterally located (51.8–90%), ground glass (41–56.4%) and consolidation (43–56%) images[4,7,8]. A retrospective diagnostic report evaluating the thoracic CT images of 130 patients found that ground-glass appearances were prevalent in the first 7-day period. In contrast, consolidation images were significantly predominant in a period longer than seven days[20]. In addition, some postmortem evaluations suggest that these findings may be caused partly by intravascular coagulation, inflammation, and necrosis[21]. However, the clinical significance of thoracic CT images in terms of outcome is still under dispute. While previous research suggested that mortality was higher in patients with advanced scores of thoracic CT, our study noted a significant difference between the patients with severe clinical manifestations and those who were discharged. In a disease with mortality, thoracic CT score tends to be higher. Cox regression analysis showed that thoracic CT score could be associated with survival, but the multivariate analysis did not reveal any significant differences due to an insufficient number of patients. Further research is warranted to obtain more revealing data in this respect. The existence of different CT scores studied by different teams also prevents standardization[8,20]. We believe that diagnostic imaging methods evaluated with the appropriate sample size may be a better determinant in predicting outcomes. On the other hand, radiation to which the patient will be exposed and complications of radiopaque materials are beyond the scope of this study.

Age, DM, HT, thoracic CT score, lymphocyte count, and AST values were defined to significantly affect survival in the univariate model of the Cox regression analysis. In contrast, these values did not stand out in the multivariate model. Although these values are promising, the limited number of patients in our study hinders the achievement of a statistically significant result. More appropriate models can be established with a larger number of participating patients.

There are some limitations of our study. The major one is its retrospective nature. The second limitation is the limited number of our study population. However, despite the relatively small sample size, the similarity of our findings with many other studies increases the reliability

of our data. Since our healthcare facility provides tertiary care, outpatients admitted to our ED are fewer in number than in other public hospitals, which explains the underlying reason for our restricted study population. Another weakness that could have affected our results is that some patients presenting to our institution by referral or their own will after the first examinations were performed in external centers were not re-tested in our healthcare center. The clinical information of these patients was excluded from the study. Patient admissions to our emergency department have decreased after mid-May, affecting our decision on the study's period.

Conclusion

The cTnT values at admission and during a hospital stay can be associated with non-survivors, especially ICU patients. Additionally, thoracic CT scores are higher in ICU admissions and tend to be higher in non-survivors. However, despite the clinical aspect, neither the cTnT values nor the thoracic CT score has a significant statistical effect on survival, even if their distributions are different between survived and non-survived groups. Further large-scale research is warranted to present an accurate and more comprehensive picture.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Evaluation of Migraine Frequency in Patients with Psoriasis

Psoriasisli Hastalarda Migren Sıklığının Değerlendirilmesi

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ABSTRACT

Aim: *Psoriasis, previously thought to be a disease restricted to the skin, is now considered systemic, accompanied by numerous comorbidities. Our study aimed to establish the migraine frequency in psoriasis patients and assess the relationship between the severity and duration of psoriasis and the frequency and severity of migraine.*

Material and Method: *This case-control study was performed in the dermatology outpatient clinic. A total of 80 people, including 40 patients over the age of 18 who applied to the outpatient clinic and were diagnosed with psoriasis, and 40 people with similar gender and age characteristics and other skin problems, were included in the control group.*

Results: *The frequency of migraine in psoriasis patients was 35.0% and 15.0% in the control group. In psoriasis patients, the median Psoriasis Area and Severity Index (PASI) score was 3.60 (1.20–13.20) in patients without migraine and 2.90 (1.20–12.00) in patients with migraine. Migraine frequency was 45.0% in patients suffering from the disease for more than eight years and 25.0% in patients suffering for eight years or less. The incidence of migraine was significantly higher in patients with psoriasis for more than eight years than in the control group.*

Conclusion: *Our study presented important outputs that the severity and duration of psoriasis disease might be related to migraine disease.*

Key words: *psoriasis; inflammation; vascular; migraine*

ÖZET

Amaç: *Deride sınırlı bir hastalık olduğu düşünülen psoriazis, günümüzde pek çok komorbiditenin eşlik ettiği sistemik bir hastalık olarak kabul edilmektedir. Çalışmamız psoriazis hastalarında migren sıklığını belirlemeyi ve psoriazis şiddeti ve süresi ile migrenin sıklığı ve şiddeti arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.*

Materyal ve Metot: *Bu kesitsel çalışmaya dermatoloji polikliniğine başvuran ve psoriasis tanısı alan 18 yaş üstü 40 hasta ile benzer cinsiyet ve yaş özelliklerine sahip 40 sağlıklı gönüllü olmak üzere toplam 80 kişi dahil edildi.*

Bulgular: *Psoriazis hastalarında ve kontrol grubunda migren sıklığı sırasıyla %35,0 ve %15,0 idi. Psoriazis hastalarında ortanca Psoriazis Alan ve Şiddet İndeksi (PASI) skoru migreni olmayan hastalarda 3,60 (1,20–13,20), migrenli hastalarda 2,90 (1,20–12,00) idi. Migren sıklığı sekiz yıldan uzun süredir hastalığı olan hastalarda %45,0, sekiz yıl ve daha az süredir devam eden hastalarda ise %25,0 idi. Sekiz yıldan uzun süredir psoriazisi olan hastalarda migren insidansı kontrol grubuna göre anlamlı olarak daha yüksekti.*

Sonuç: *Çalışmamız psoriazis hastalığının şiddeti ve süresinin migren hastalığı ile ilişkili olabileceğine dair önemli veriler sunmaktadır.*

Anahtar kelimeler: *psoriasis; inflamasyon; vasküler; migren*

Introduction

Psoriasis, previously thought to be a disease restricted to the skin, is now considered systemic, accompanied by changes caused by chronic inflammation and numerous comorbidities[1]. In particular, the risk of developing severe vascular incidents like cardiovascular and cerebrovascular diseases is high[2]. Most of the publications have focused on cardiovascular and metabolic diseases[3]. Comorbidities accompanying psoriasis include psoriatic arthritis (PsA), autoimmune diseases, sleep apnea, non-alcoholic steatohepatitis, and chronic obstructive pulmonary disease[1,4]. Besides, cardiovascular risk factors

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such as hypertension (HT), diabetes (DM), dyslipidemia, obesity, and metabolic syndrome are increasing[5].

Studies in recent years have shown that psoriasis is accompanied by neurological or psychiatric diseases such as multiple sclerosis, epilepsy, migraine, depression, anxiety, suicidal behavior, etc.[6].

The incidence of psoriasis in both genders is similar, and its incidence is around 2% worldwide[7].

In addition to the known comorbidities of psoriasis, migraine is morbidity whose etiology is not fully understood, and its relationship with psoriasis cannot be demonstrated. Migraine is a common neurological disease characterized by headaches, nausea, and vomiting, which occur due to excessive cortical stimulation and afferent trigeminovascular sensitization. It can last 4–72 hours, be moderate to severe in attacks, and increase with physical activity, light, and noise[8,9]. By an analysis from the Global Burden of Disease (2016) study, the global migraine frequency is approximately 14.4%, with 18.9% in females and 9.8% in males[10]. Some cytokines (such as nitric oxide, tumor necrosis factor-alpha, and adipokines (leptin and adiponectin)) that play an essential role in the etiopathogenesis of psoriasis may cause meningeal inflammation, vasospasm, and hypersensitivity in pain pathways in patients with migraine[11].

In a study conducted in Italy on the psoriatic population, it has been determined that the risk of migraine is increased in both gender groups, mostly in females[12]. In a study conducted with 163 psoriasis patients in Türkiye, 8.5% had a migraine[8].

Very few studies examine the relationship between psoriasis and migraine globally and in our country. Our study aimed to establish the migraine frequency in psoriasis patients and evaluate the relationship between the severity and duration of psoriasis disease and the frequency and severity of migraine disease.

Material and Methods

This case-control study was performed between January 2019 and March 2020. Forty people who were diagnosed with psoriasis, over the age of 18 and accepted to participate in the research, who applied to the dermatology outpatient clinic were included, and 40 people with similar gender and age characteristics but without a diagnosis of psoriasis and who applied to the dermatology outpatient clinic due to other skin problems, were included in the control group. It was evaluated whether the patients had a previous diagnosis of migraine in the electronic registry system according to ICD 10. After confirmation by asking those diagnosed in the system, they were included as cases of migraine.

The local ethics committee approved the study.

In the study, the sociodemographic features of the participants (age, gender, body mass index (BMI)) were determined. In assessing the severity of psoriasis, the "Psoriasis Area and Severity Index" (PASI), which evaluates the severity and prevalence of the disease together, was used. The maximum score of PASI is 72[13].

In addition, the duration of the disease, the presence of diabetes mellitus (DM), hypertension (HT), and migraine was questioned. According to the Migraine Disability Assessment Scale (MIDAS) scores for migraine disease; the patients were grouped as follows:

Group 1: Little or no disability (Loss for 0–5 days),

Group II: Mild disability (Loss for 6–10 days),

Group III: Moderate disability (Loss for 11–20 days)

Group IV (21+ days): Severe disability. This group could not be evaluated because no patient had a Grade IV disease[14].

SPSS 25 package program was used for statistical analysis. Descriptive statistical analyses were conducted to evaluate the data; the Kolmogorov-Smirnov test was used for normality tests, the Chi-square test when comparing the categorical data, and the Mann-Whitney U test when comparing age, BMI, and PASI scores of groups and the duration of the disease. In addition, a correlation test was used to determine the relationship between PASI score, duration of disease, and migraine severity. The statistical significance level was defined as $p<0.05$.

Results

Fifty percent (40) of the participants were females; the mean age was 43.98±15.60 years. Of the patients with psoriasis, 47.5% (19) were females, the mean disease duration was 11.15±9.09 (min-max: 1–31 years), and the mean PASI score was 5.31±4.10. Migraine was present in 25.0% (20) of all participants. The descriptive characteristics of the participants according to the presence of migraine in psoriasis and control groups are given in Table 1. The differences were not statistically significant when psoriasis patients and control groups were compared regarding age, gender, BMI, and the presence of chronic disease (DM, HT). When these variables were compared between the patients with and without a migraine in the psoriasis group, a statistically significant difference was found only in the BMI variable (Table 1). When the presence of DM and HT in the psoriasis patient group was compared, no statistically significant difference was found between the two diseases ($p=0.338$). The frequency of migraine in psoriasis patients was 35.0%, and it was 15.0% in the control group, which was not statistically significant ($p=0.069$).

A moderate positive correlation was found between PASI score and MIDAS in psoriasis patients (Table 2).

Table 1. *Descriptive characteristics of the participants according to the presence of migraine in psoriasis and control groups*

	Psoriasis patient group				Control group			
	With migraine (n=14)	Without migraine (n=26)	Total (n=40)	p[1]	With migraine (n=6)	Without migraine (n=34)	Total (n=40)	p[2]
Gender								
Female (n)	8	11	19	0.370[a]	5	16	21	0.823[a]
Male (n)	6	15	21		1	18	19	
Age (Mean, SD)	37.07 (12.11)	47.27 (17.69)	43.70 (16.55)	0.100[b]	47.17 (12.92)	43.74 (15.20)	44.25 (14.78)	0.851[b]
BMI (Mean, SD)	22.95 (3.11)	27.49 (4.91)	25.90 (4.85)	0.004[b]	26.99 (4.82)	27.27 (4.09)	27.23 (4.14)	0.142[b]
DM (n)	0	3	3	0.539[a]	1	2	3	1.000[a]
HT (n)	1	4	5	0.640[a]	0	6	6	1.000[a]
PASI (Mean, SD)	4.85 (4.11)	5.55 (4.15)	5.31 (4.10)	0.477[b]	-	-	-	-
Disease duration (years) (Mean, SD)	13.14 (8.55)	10.08 (9.35)	11.15 (9.09)	0.186[b]	-	-	-	-

1 Comparison of patients with and without a migraine in the patient group with psoriasis 2 Comparison of psoriasis patient and control group a Chi-square and Fisher tests b Mann-Whitney U test

Table 2. *Correlation of PASI score with age, BMI, disease duration, and MIDAS in patients with psoriasis*

	PASI-Age	PASI-BMI	PASI-Disease duration	PASI-MIDAS
r	0.225	-0.039	-0.102	0.525
p	0.163	0.812	0.529	0.022
N	40	40	40	14

When the presence of migraine in psoriasis patients and the PASI score were compared, the median PASI score was found to be 3.60 (1.20–13.20) in psoriasis patients without, while it was 2.90 (1.20–12.00) in psoriasis patients with migraine. However, this difference was not statistically significant (Fig. 1).

When the presence of migraine in psoriasis patients was evaluated according to the duration of the disease, migraine was observed in 45.0% of the patients suffering from the disease for more than eight years. In patients suffering from the disease for eight years or less, migraine frequency was 25.0%. Although the presence of migraine was higher in patients with longer disease duration, this difference was not statistically significant (χ^2=0.989, p=0.320). However, this difference was significant between the control group and those with psoriasis for more than eight years (χ^2=6.40, p=0.041).

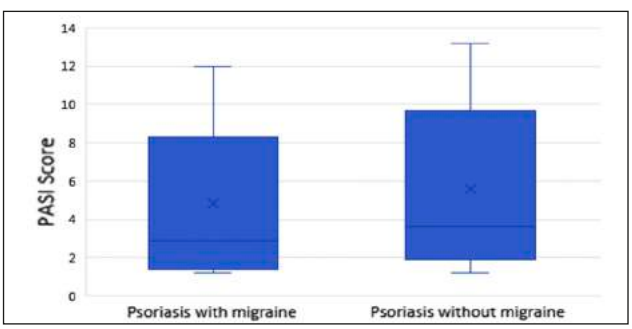

Figure 1. *PASI Score according to the presence of migraine in patients with psoriasis (Mann-Whitney U Test: Z=-0.711; p=0.477).*

Discussion

Although the prevalence of psoriasis varies according to different races and the region of residence, it is widespread worldwide[15]. It is seen less commonly in Asia than in western countries[16]. It is more common in northern countries than in tropical countries[17]. Norway, a northern country, is one of the countries where psoriasis is common globally at 4.8%[18].

Various studies show that the incidence of psoriasis in our country varies between 0.7 and 5.18%[19,20].

Many studies indicate that the incidence of psoriasis is equal in both genders[15,21]. In our study, psoriasis was found to be more common in males, albeit with a slight difference, compared to females. Consistent with our research, studies are reporting male predominance in psoriasis[8].

In a study conducted in Italy, the mean age of patients with migraine and psoriasis was higher than that of patients with only psoriasis[12]. In a study conducted in Türkiye, the mean age of patients with migraine was lower than that of patients without migraine. This difference was also found to be statistically significant[8]. In our study, the mean age of psoriasis patients without migraines, was lower, but it was not statistically significant.

Many comorbidities accompany psoriasis. In its etiopathogenesis, proinflammatory cytokines cause atherogenesis and peripheral insulin resistance[15]. Therefore, it poses a risk for DM and HT. DM and HT are more common in psoriasis patients[2]. In studies, DM and HT are seen frequently in psoriasis patients[3,15]. In our study, these diseases were found at a higher rate in psoriasis patients than in the control group, which was consistent with other studies, but the difference was insignificant.

A meta-analysis study, obesity was correlated to the frequency and severity of psoriasis. Looking at the relationship between psoriasis and obesity in this study, the estimated relative risk for obesity among patients with severe psoriasis was 2.23 (95% CI: 1.63–3.05), while it was 1.46 (95% CI: 1.17–1.82) in the mild type. In addition, this study shows that the prevalence of obesity increases by more than 50% in those with psoriasis compared to those without[22]. In our study, there was no significant difference between the psoriasis patient group and the control group regarding BMI, and there was no correlation between BMI and PASI. Following our study, no statistically significant relationship was found between PASI and BMI in a study conducted in Ankara[23].

Obesity also creates a risk for migraines. Although some studies have stated that BMI does not increase the frequency of migraines, it has been shown that BMI is related to the frequency and severity of migraine attacks[24]. In a study conducted in Italy, no difference was found in obesity in psoriasis patients with and without migraines[12]. In a study conducted in Diyarbakir, Türkiye, the obesity rate was 14.2% in patients with migraines and 19.4% in patients without[8]. In our study, the mean BMI was higher in patients with psoriasis without migraine than in patients with migraine, and this difference was significant.

In a study conducted in Korea, the rate of migraine (3.3%) was higher in psoriasis patients compared to the control group (2.9%) [25]. In our study, the frequency of migraine in psoriasis patients was 35.0% and 15% in the control group, although this difference was statistically insignificant (p=0.069).

Even though not statistically significant in our study, the PASI score was higher in psoriasis patients without migraine than in psoriasis patients with migraine. In another study, the mean PASI score was 11.52±7.6 in patients with migraine and 13.1±10.1 in the group without a migraine, concordance with our study[8].

In our study, when the correlation between PASI score and age, BMI, disease duration, and MIDAS in patients with psoriasis was examined, only a moderate positive correlation was found with MIDAS. The lack of studies investigating the relationship between PASI and MIDAS in the literature can be seen as a different aspect of our study.

Among the factors affecting the quality of life of psoriasis patients, the duration of the disease is as effective as its severity[26]. Our study showed a significant difference in migraine frequency between patients with disease duration longer than eight years and the control group. However, no correlation was found between disease duration and severity.

Limitations

One of the limitations of our study was that the participants of our study consisted only of patients who applied to the outpatient clinic, so it could not be generalized to the whole population. The fact that risk factors closely related to inflammatory conditions such as smoking, alcohol, and exercise have not been questioned is a limitation to revealing the incidence of migraine more clearly. Finally, since it was designed as an observational study, the inability to specify a precise causality is also a limitation.

Conclusion

Psoriasis is a disease that accompanies many diseases and is effective in forming many diseases. Migraine is one of these diseases. However, we found no difference in the frequency of migraine in psoriasis patients compared to the control group, the severity, and duration of the disease presented important outcomes indicating that it may be associated with migraine disease. More comprehensive studies, including lifestyle factors, will reveal the causality better in the future. In addition, more studies should be conducted on the relationship between psoriasis and migraine disease in our country.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Is There a Beneficial Effect of Single Dose Antenatal Steroid Therapy on Mortality and Morbidities in Infants <30 Weeks Gestational Age?

Tek Doz Antenatal Steroid Tedavisi Gestasyonel Yaşı <30 Hafta Bebeklerde Mortalite ve Morbidite Üzerine Etkili mi?

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ABSTRACT

Aim: *Our knowledge regarding the impact of single-dose antenatal corticosteroid treatment on neonatal morbidities of VLBW is still scarce. In this study, we aimed to evaluate outcomes of infants born <30 weeks' gestation that received no ACS, partial course of ACS, and complete course of ACS.*

Material and Method: *In this retrospective study, infants <30 weeks in gestation at birth were included and divided into three groups based on exposure to ACS; Group 1, infants born without ACS exposure, Group 2, infants born after exposure to one dose of betamethasone, Group 3, infants born after exposure to complete the course. Our primary outcome was mortality. Secondary outcomes included the following: PDA, NEC, severe IVH, bronchopulmonary dysplasia, and cystic periventricular leukomalacia (PVL).*

Results: *616 infants were included. The incidence of chorioamnionitis was significantly higher in the complete course ACS group (p<0.05). The mortality rate was highest in the no ACS group (16.0%) compared to other groups but not statistically different. There was a trend toward lower morbidity in the partial course ACS group compared to none.*

Conclusion: *We found no statistically significant benefit of incomplete antenatal corticosteroids in infants born <30 weeks' gestation.*

Key words: *antenatal corticosteroids; betamethasone; neonatal outcomes; very low birth weight infants*

ÖZET

Amaç: *Acil nedenlerle çok düşük doğum ağırlıklı (ÇDDA) bebeklerin önemli bir kısmı tam doz antenatal kortikosteroid tedavisi tamamlanamadan doğsa da, kısmi doz antenatal kortikosteroid (AKS) tedavisinin ÇDDA'lı hastaların neonatal mortalite ve morbiditeleri üzerine etkisine ilişkin bilgilerimiz hala kısıtlıdır. Bu çalışmada, <30 hafta doğan; AKS uygulanmayan, kısmi doz AKS ve tam doz AKS uygulanan bebeklerin sonuçlarını değerlendirmeyi amaçladık.*

Materyal ve Metot: *Bu retrospektif çalışmaya doğum haftası <30 hafta olan bebekler dahil edildi ve AKS uygulanma durumuna göre üç gruba ayrıldı; Grup 1, AKS uygulanmadan doğan bebekler, Grup 2, tek doz betametazon uygulanan bebekler, Grup 3, tam doz AKS uygulanan bebekler. Birincil sonucumuz mortalite idi. İkincil sonuçlar: PDA, NEK, şiddetli IVK, bronkopulmoner displazi ve kistik periventriküler lökomalazi (PVL) olarak belirlendi.*

Bulgular: *616 bebek çalışmaya dahil edildi. Koryoamniyonit sıklığı tam doz AKS grubunda anlamlı olarak daha yüksekti (p<0,05). Mortalite oranı AKS uygulanmayan grupta diğer gruplara kıyasla en yüksek olarak bulunda (%16,0) ancak istatistiksel farklılık bulunmadı. Kısmi doz AKS grubunda, AKS uygulanmayan gruba kıyasla neonatal morbidite sıklığı düşme eğiliminde idi.*

Sonuç: *Sonuç olarak, <30 hafta doğan bebeklerde eksik doz antenatal kortikosteroid tedavisinin anlamlı faydası saptanmadı.*

Anahtar kelimeler: *antenatal kortikosteroid; betametazon; çok düşük doğum ağırlıklı bebek*

Introduction

Despite significant improvements in perinatal care, preterm birth is still one of the leading causes of neonatal morbidity and mortality. Since Liggins's study in 1972[1] demonstrated antenatal corticosteroids (ACS) effect on reducing respiratory distress syndrome (RDS) and mortality in premature births before 34 gestational weeks, ACS has become a mainstay component in the management of cases of premature delivery.

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Several studies showed that antenatal administration of corticosteroids accelerates lung maturation and increases surfactant production in the fetal lungs[2,3]. Moreover, Schwab also demonstrated that in addition to preventing RDS, ACS has vasoconstrictive effects on fetal cerebral blood flow and protects the fetus against intraventricular hemorrhage (IVH)[4]. A recent Cochrane systemic review in 2021, including 30 randomized controlled studies, confirmed that after a single course of ACS, the risk of moderate to severe RDS, IVH, and neonatal death in preterm infants significantly reduced by 43.14, and 26%, respectively[5].

Although the most significant beneficial effects of ACS are shown if ACS is administered between 24 hours and less than seven days before actual delivery[6], a significant population of premature infants would not receive the complete course due to maternal or fetal indications that lead to emergency or imminent delivery. While some studies have demonstrated that a partial course of ACS can reduce morbidity, the literature yielded inconsistent results[7,8]. So far, few studies have primarily focused on assessing the neonatal effects of an incomplete course of ACS on very low birth weight infants (VLBW). Therefore, the literature on the effect of partial course antenatal corticosteroid therapy on VLBW morbidity is still scarce.

In this retrospective cohort study, we aimed to evaluate outcomes of infants born <30 weeks' gestation that received no ACS, partial course of ACS, and complete course of ACS. We sought to demonstrate whether administering a partial course of ACS would benefit mortality or other neonatal outcomes.

Material and Methods

This retrospective cohort study was conducted between January 2014 and October 2017 in a single Level III Intensive Care unit at the Zekai Tahir Burak Women's Health and Children Hospital, Ankara, Türkiye. Hospital Research Ethics Committee approved the study.

Infants <30 weeks in gestation at birth (based on early ultrasound (US) or last menstrual period if the US is not available) who were born in our hospital were considered eligible for inclusion. Infants with congenital or chromosomal anomalies, severe perinatal asphyxia, and whose data were missing were excluded from the study.

Since the current data concerning ACS are insufficient to recommend one steroid over the other, there are considerable differences between countries regarding antenatal corticosteroid choice. At our institution, according to the current recommendation by the American College of Obstetricians and Gynecologists[6], two intramuscular doses of 12 mg of betamethasone are administered 24 hours apart to women who are at risk of premature labor between 24 and 34 weeks gestational age.

Infants were divided into three groups based on exposure to ACS; Group 1, infants born without ACS exposure; Group 2, infants born after exposure to one dose of betamethasone, Group 3, infants born after exposure to complete the course.

The main clinical characteristics such as gestational age, birth weight, gender, delivery mode, 5 minutes Apgar score, requiring delivery room resuscitation (either required endotracheal intubation or other further interventions, such as chest compressions and medications), and the number of twin births, were obtained from medical records. In addition, maternal history of pregnancy-induced hypertension, prolonged rupture of membranes (PROM) (>18 h), and evidence of chorioamnionitis were also recorded. Chorioamnionitis is defined as maternal fever ≥38°C not explained by another source of infection and one or more of the following signs: maternal tachycardia (100 beats per minute (bpm) or more), fetal tachycardia (>160 bpm), white blood cell count of 20000 μL or more, uterine tenderness and foul odor upon delivery of the infant[9].

Our primary outcome was mortality, defined as death before hospital discharge. Secondary outcomes included the following: surfactant administration, patent ductus arteriozus (PDA) requiring either medical or surgical treatment, NEC stage II or more of modified Bell's criteria[10], severe IVH[11], bronchopulmonary dysplasia (BPD), and cystic periventricular leukomalacia (PVL). Two composite outcomes were prespecified: BPD or death and one consisting of intraventricular hemorrhage, cystic PVL, or death. RDS was defined within the first 72 hours to have clinical signs of respiratory distress, including tachypnea, retractions, grunting, or cyanosis with increasing oxygen requirements and diagnostic radiological findings[12]. Jobe classification is used to define BPD, which is defined at the PM 36th week for preterms born before 32 weeks of gestation and on the postnatal 28th day for preterms born at or after 32 weeks of gestation or at the time of discharge, whichever occurs earlier, treatment with oxygen >21% for at least 28 day regardless of the clinical severity of respiratory failure due to RDS or other reasons in the first days of life[13]. Mild BPD cases included breathing room air at 36-week PMA or discharge, whichever comes first excluded. Incidence of pneumothorax, duration of mechanical ventilation and total respiratory support, and length of hospital stay were also recorded.

Statistical Analysis

Infants were classified into three groups according to their ACS exposure. Based on the outcome parameters, these groups were compared. Data were analyzed using SPSS, version 22.0 (SPSS, Chicago, IL). Categorical variables were expressed as percentages and compared

using Pearson's chi-squared and Fisher's exact tests when necessary. Mean, and standard deviation (SD) were used as descriptive variables for continuous variables. These variables were analyzed with the ANOVA test since the parameters are normally distributed. We used a logistic regression model adjusting for the effects of clinical chorioamnionitis to estimate the adjusted odds ratios (ORs) and measure the 95% CI for comparing the three groups regarding the primary and other outcomes. A p-value <0.05 was considered significant.

Results

We assessed 681 infants <30 weeks in gestation at birth during the study period. After excluding 65 infants for missing data, 616 infants were included in the study. There were 274 (44.4%) infants in the complete course, 143 (23.2%) in the partial course, and 199 (32.4%) in the no ACS group.

The demographic characteristics of the infants according to steroid exposure are summarized in Table 1. The three groups did not differ for gestation age, birth weight, gender, 5th minute APGAR score, number of twin gestations, maternal hypertension, and PROM. However, infants who received no ACS were likely to need resuscitation at the delivery room compared to the partial and complete course ACS groups ($p<0.05$). Also, the incidence of chorioamnionitis was significantly higher in the complete course ACS group compared to the other two groups ($p<0.05$).

The incidence of surfactant instillation in the complete course group was 48.2%, significantly lower than the partial course and no ACS group (67.2%, 64.3%, respectively) ($p<0.05$). The mortality rate was higher in the no ACS group (16.0%) compared to the partial and complete course group (14.6% and 12.4%), but it was not statistically different ($p>0.05$). There were no significant differences between the no ACS and partial ACS groups in terms of mortality, IVH, composite outcome of BPD or death, and IVH/cystic PVL or death, despite lower morbidity rates in the partial ACS group. The incidence of PDA, severe ROP and NEC were similar between groups (Table 2). A logistic regression model was designed to control clinical chorioamnionitis to compare three groups in terms of mortality, IVH and the composite outcome of BPD or death, and IVH/cystic PVL or death. Similar to univariate analysis, no statistical difference was found between groups.

Discussion

In this study, we sought to compare outcomes of infants born <30 gestational weeks exposed to different doses of antenatal corticosteroids to show whether administering an incomplete course of ACS would benefit short-term and long-term morbidities and mortality. Our results demonstrated that among our cohort of preterm infants, there was a significant decrease in the need for surfactant treatment after exposure to a complete course of ACS, in line with previous studies[14]. Additionally, there was a trend towards less morbidity in the partial course ACS group versus none, but the difference was not statistically significant.

If administered a complete dose seven days before delivery in women at risk of preterm birth, the substantial beneficial effects of antenatal steroids are evident. The Latest Cochrane review has suggested that no further randomized clinical trials are needed to demonstrate the effect of the current recommended antenatal corticosteroid regime[5]. Nevertheless, since the current recommended regime of antenatal betamethasone was suggested in 1972 by Liggins and Howie[1], clinical trials testing different dose regimens have never been performed. Schmidt et al. showed that single-dose intramuscular betamethasone significantly improved lung compliance and gas exchange in preterm lambs[15]. Similarly, Ballard et al. demonstrated that one dose of betamethasone benefits early pulmonary function. A single dose of betamethasone 48 hours before delivery increased the maximum lung volume and dynamic compliance of preterm sheep[16]. Also, the latest good practice recommendations of FIGO Working Group for Preterm Birth included administration of antenatal corticosteroids even if preterm birth is expected within 18 hour[17]. However, the literature on the impact of a partial course of ACS on VLBW preterm infants still needs further investigation, as few studies compare the outcomes of infants born following a single betamethasone dose.

Retrospective studies on this subject included different gestational age ranges and yielded inconsistent results so far[8,18]. Although our study found the incidence of delivery room resuscitation decreased among infants exposed to a partial course of ACS, it failed to find a statistically significant reduction in neonatal morbidities following single-dose betamethasone administration compared to the no exposure group. In contrast to our study, Chawla et al. demonstrated that infants exposed to a single dose of ACS had a significantly lower incidence of IVH than those without ACS[18]. However, the overall IVH rate was significantly higher in that study than ours, possibly due to the cohort's lower mean gestational age and birth weight, especially in the no ACS group. Probably higher gestational age of our cohort resulted in lower IVH incidence in all groups and did not enable us to reach statistical significance. Elimian et al. reported a lower need for vasopressors, IVH, and mortality rate in the partial course ACS group[7]. However, the study included neonates born at 23–24

Table 1. *Maternal and infant characteristics of study groups*

	No ACS (n=199)	Partial (n=143)	Complete (n=274)	p value
Gestational age (weeks) (SD)	28±1.5	28.1±1.2	28.2±1.2	0.67
Gender (male) n (%)	104 (52.3)	68 (47.6)	145 (52.9)	0.56
Birth weight (grams) (SD)	1067±242	1052±230	1058±228	0.2
Apgar, 5. min (<5), n (%)	12 (6)	3 (2.1)	9 (3.3)	0.14
Cesarian section n (%)	166 (83)	118 (82.5)	236 (86.1)	0.56
PIH n (%)	37 (18.5)	30 (20)	52 (18.9)	0.84
Chorioamnionitis n (%)	19 (9.5)	11 (7.7)	50 (18.2)	0.01
Resuscitation in delivery room, n (%)	61 (30)	41 (28)	58 (21.2)	0.047
PROM (>18 h) n (%)	31 (15.5)	20 (13.9)	67 (24.4)	0.07
Twin gestation n (%)	50 (25.1)	34 (23.8)	59 (21.5)	0.64

Partial group includes one dose of betamethasone. Complete group includes two doses of betamethasone. *Plus-minus values are mean ± standard deviation SD: standard deviation, p values <0.05 were considered significant. ACS: antenatal corticosteroid, PROM: prolonged rupture of membranes, PIH: pregnancy induced hypertension.

Table 2. *Association of ACS dosing and clinical outcomes of the study infants*

	No ACS (n,%)	Partial (n,%)	Complete (n,%)	p value
Surfactant administration	123 (67.2)	92 (64.3)	132 (48.2)	0.04
PDA	80 (40.2)	64 (44.7)	92 (33.5)	0.2
Pneumothorax	4 (2)	5 (3.4)	6 (2.1)	0.2
BPD	32 (16)	19 (13.2)	33 (12)	0.32
IVH	25 (12.5)	20 (11.4)	25 (9.1)	0.42
PVL	20 (10.1)	16 (11.1)	20 (7.2)	0.38
NEC	3 (1.5)	5 (3.4)	5 (1.8)	0.62
BPD or death	58 (29.1)	36 (25.1)	63 (23)	0.18
IVH/PVL or death	42 (21.1)	31 (21.6)	50 (18.3)	0.34
Death	32 (16.0)	21 (14.6)	34 (12.4)	0.28
Duration of MV d, (SD)	4.3±7.9	4.5±8.9	3.4±7.7	0.62
Duration of respiratory support, d, (SD)	13.2±12.5	12.9±14.6	12.6±13.4	0.46
Duration of hospital stay d, (SD)	58.7±32.3	58.6±29.9	56.3±30.7	0.53

Partial group included one dose of betamethasone. Complete group included two doses of betamethasone. SD: standart deviation, p values <0.05 were considered as significant. PDA=patent ductus arteriozus, BPD: bronchopulmonary displasia, IVH: intraventricular hemorrhage, PVL: periventrivular leucomalacia, NEC: necrotizing enterocolitis, MV: mechanical ventilation.

gestational weeks with a high mortality rate, which was different from our study population. Like our findings, Costa et al. demonstrated no significant difference in NEC, IVH, and mortality among infants exposed to single-dose betamethasone[8]. Nevertheless, a subgroup analysis showed that one dose of ACS was clinically comparable to the complete dose in the 25–27 weeks subgroup. Salhab et al. included extremely low birth weight infants ≤1000 gr and confirmed that beneficial effects of ACS were dose-dependent as they found no significant differences between the no ACS and partial course ACS group in terms of neonatal outcomes. However, in line with our study, they demonstrated a trend towards less morbidity in the partial course ACS group[19]. Similarly, a multicenter, prospective observational study analyzing the effect of ACS on mortality in preterms 23 to 28 weeks gestational age found only a complete course of ACS administration associated with a reduction in mortality and BPD[20].

A recent study on an animal model suggested that duration of exposure to low-dose ACS rather than total exposure mediates lung maturation[21]. Although it is recommended to start a course of antenatal corticosteroids for all women at high-risk premature delivery, even if only one dose is anticipated[22], a study showed that exposure to ACS at least 24–48 h before delivery reduces the incidence of RDS more significantly[23]. Since our report was designed retrospectively and the data on the timing of ACS before delivery was not noted, we could not analyze the effect of duration of fetal exposure that might have a role in our results. Additionally, it is possible that the underlying cause of emergent premature birth, which resulted in the inability to administer the complete course of ACS, also has a role in neonatal outcomes and increases the risk of morbidities. Perhaps a prospective randomized trial examining whether a single dose is non-inferior to the maximum dose in preventing neonatal complications will adequately address some of these questions[24].

In our study, clinical chorioamnionitis was more common in the complete course ACS group compared to others. A previous study suggests maternal and neonatal infection rates do not increase with antenatal corticosteroid administration[25]. Nonetheless, caution is needed when using ACS in the presence of chorioamnionitis. As antenatal infection is one of precipitating factors of preterm birth, attention must be paid to avoid increasing maternal infection risk while preventing preterm labor. Waterberg et al. found that chorioamnionitis increased neonatal morbidities in VLBW infants[26]. Interestingly, we designed an additional logistic regression model controlling clinical chorioamnionitis among groups in terms of mortality, IVH, and the composite outcome of BPD or death, IVH/cystic PVL or death, and the results did not differ.

There are several limitations of our study. Although our sample size was larger than similar studies[7,8,17,18], it was a single-center study. It was conducted retrospectively, and the underlying cause of preterm delivery and the timing of antenatal corticosteroid administration was not specified.

Conclusion

In conclusion, our study results suggest that although statistically insignificant, there was a trend of less morbidity in the partial course ACS group. As a result, we believe that even a single dose of betamethasone should be administered to every patient at risk of preterm delivery, even if the delivery cannot be delayed until the administration of the second dose. We also think further studies targeting subpopulations of preterms are needed to show the benefit of partial course antenatal corticosteroids for different gestational age subgroups.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Older Geriatric Patients Consulting the Thoracic Surgery Clinic from the Emergency Department During COVID-19

COVID-19 Sürecinde Acil Servisten Göğüs Cerrahisi Kliniğine Başvuran Yaşlı Geriatri Hastalarının Değerlendirmesi

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ABSTRACT

Aim: *This study was designed to examine the applications of geriatric patients aged 80 and over to emergency service for trauma and non-traumatic reasons and to evaluate the relationship between those findings and the restrictions applied due to the COVID-19 pandemic.*

Material and Method: *A total of 111 patients over the age of 80, including 49 patients who were directed from the emergency room to thoracic surgery due to thoracic trauma and 62 patients who were referred to thoracic surgery for non-traumatic reasons, were included in the study between March 2020 and March 2021.*

Results: *During the pandemic period in question, it was found that female patients were admitted to the emergency department due to trauma statistically significantly more often while male patients were more often admitted to the emergency department for non-traumatic reasons (p=0.021). It was furthermore found that 22 (44.9%) of the 49 patients who presented with trauma were hospitalized, while 10 (16.1%) of the 62 patients who presented for non-traumatic reasons were hospitalized (p=0.001).*

Conclusion: *We know that the course of disease of many patients, especially patients with malignancies, continues to progress with the frequent occurrence of chronic diseases or diseases with asymptomatic and progressive characteristics in the geriatric population. At the same time, pandemic restrictions may cause difficulties in reaching the hospital. For this reason, we advise that the geriatric population, especially older geriatric patients, not delay hospital visits in the face of any other pandemic-related restrictions that may be applied. The general public should also be made aware of this issue. Otherwise, the social inactivity imposed as a result of such pandemic-related restrictions may increase the mortality rate among geriatric patients due to chronic diseases or neoplasias far beyond the mortality rate that occurs due to the pandemic itself.*

Key words: *geriatrics; covid-19; pandemic; thoracic trauma*

ÖZET

Amaç: *Bu çalışmada pandemi sürecinde 80 yaş ve üstü geriatrik hastaların travma ve travma dışı sebeplerle acil servise başvurularının incelenmesi ve çıkan sonuçların, pandemi sebebiyle uygulanan kısıtlamalar ile ilişkisinin değerlendirilmesi amaçlanmıştır.*

Materyal ve Metot: *Çalışmaya Mart 2020-Mart 2021 tarihleri arasında 80 yaş üstü toraks travması sebebiyle acil servisden göğüs cerrahisine danışılan 49 hasta ile travma dışı sebeplerle göğüs cerrahisine danışılan 62 hasta olmak üzere toplam 111 hasta dahil edilmiştir.*

Bulgular: *Söz konusu pandemi döneminde kadın hastaların istatistiksel olarak anlamlı derecede daha sık travma nedeniyle acil servise başvurdukları, erkek hastaların ise travma dışı nedenlerle acil servise daha sık başvurdukları saptandı (p=0,021). Pandemide travma ile başvuran 49 hastanın 22'sinin (%44,9), travma dışı nedenlerle başvuran 62 hastanın 10'unun (%16,1) hastanede yattığı saptandı (p=0,001).*

Sonuç: *Geriatrik nüfusta, kronik hastalıkların veya malignite gibi asemptomatik seyredip ilerleyici karakterdeki hastalıkların sık görülmesi ve pandemik kısıtlamaların hastaneye ulaşmada sıkıntı yaratması sebebiyle başta malignite hastaları olmak üzere birçok hastanın evrelerinin ilerlediğini biliyoruz. Bu sebeple bundan sonra meydana gelebilecek başka pandemi süreçlerini yönetirken geriatrik nüfusun (özellikle ileri yaş geriatrik hastaların) hastaneye başvurularını geciktirmemeleri gerektiğini ve bu hususta halkın bilinçlendirilmesi gerektiğini düşünüyoruz. Aksi takdirde gelişebilecek başka pandemilerde, geriatrik hastalara uygulanacak kısıtlamalar sonucunda toplumsal hareketsizliğin (kronik hastalıklar veya neoplazi hastalarının hastaneye ulaşmadaki gecikmeleri sebebiyle) mortaliteyi, pandeminin meydana getirdiği mortaliteye göre çok daha fazla artırabileceğini düşünüyoruz.*

Anahtar kelimeler: *geriatri; covid-19; pandemi; toraks travması*

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Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 coronavirus, led to a global crisis with its impact on human life in 2020[1]. Since the beginning of the pandemic, all possible human and material resources in hospitals have been used to combat COVID-19[2]. For this reason, various restrictions have been applied to use hospital resources more effectively and to reduce both the transmission of COVID-19 infection among people and the hospital load due to the pandemic. Many restrictions during the pandemic have been aimed at protecting the geriatric population from the virus. A curfew was applied in Türkiye to the segment of the population aged ≥65 throughout most of the pandemic. As a result of these policies, there has been a significant decrease in the admission of geriatric patients to the hospital. This study aimed to evaluate geriatric patients aged ≥80 who presented to emergency services for treatment in thoracic trauma and non-traumatic thoracic surgery clinics and compare those findings with the literature.

Materials and Methods

A total of 111 patients over the age of 80, including 49 patients who were directed from the emergency room to thoracic surgery due to thoracic trauma and 62 patients who were directed to thoracic surgery for non-traumatic reasons, were included in the study between March 2020 and March 2021. The data of the included patients were obtained by retrospectively scanning the hospital's information management system. The reasons for the admission of the patients were obtained by examining the records of consultations sent to our clinic. Patients were grouped according to the dates they presented to the emergency department. The relationship between COVID-19 waves and patients' admissions to the emergency department was statistically evaluated.

Statistical Method

Statistical analyses were performed using IBM SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA). Numerical variables were expressed as means ± standard deviations and medians (minimums-maximums), and categorical variables were expressed as numbers and percentages. Parametric test assumptions (normality and homogeneity of variance) were checked before the groups were compared in terms of numerical variables. The differences between the groups were examined using t-tests for dependent groups. Categorical values were analyzed with the Fisher exact test. Mann-Whitney U and Kruskal-Wallis tests were used to compare continuous variables. Values of $p<0.05$ were accepted as statistically significant for all analyses.

Results

In the first 12 months of the COVID-19 pandemic, 10621 consultations were sent to our thoracic surgery clinic, 2879 (27.1%) of which originated from emergency services. Of those 2879 consultations sent from the emergency department, 111 (3.85%) cases involved patients aged ≥80 years. While 49 (44.5%) of those patients presented to the emergency department due to thoracic trauma, 62 (55.5%) presented for non-traumatic reasons. Fifty-nine (53.2%) of these patients were male, and 52 (46.8%) were female. Of the patients presenting with trauma, 29 (59.2%) were female, and 20 (40.8%) were male, while 39 (62.9%) of the patients presenting for non-traumatic reasons were male and 23 (37.1%) were female. During the pandemic period, it was found that female patients were admitted to the emergency department due to trauma statistically significantly more often, while male patients were more often admitted to the emergency department due to non-traumatic reasons ($p=0.021$). However, men were more likely to present to the emergency department due to trauma during non-pandemic times. The mean age of the patients was 85.46±4.62 (range: 80–99) years ($p=0.711$). Among trauma cases, 44 (39.6%) of the patients had presented due to falling, 4 (3.6%) due to traffic accidents, and 1 (0.9%) due to assault. Among the patients who presented for non-traumatic reasons, the most common reason was pleural effusion in 44 (37.8%) cases, followed by a mixture of other more rare reasons (lung abscess, pneumomediastinum, malignancy, pneumothorax, control visits) in 18 (16.2%) cases. For 24 (54.6%) of the patients who presented with pleural effusion, the etiology was a factor causing transudative pleural fluid, while for 20 (45.4%), the etiology was a factor causing exudative pleural fluid. The etiology was loculated empyema for 10 (22.7%) patients with exudative pleural effusion samples and malignant effusion for 10 (22.7%) patients. Of the patients who presented for non-traumatic reasons, 48 (77.4%) presented with dyspnea, 5 (8.1%) had a poor general condition, 4 (6.5%) had cough, 3 (4%) had chest pain, 1 (1.6%) had hematemesis, and 1 (1.6%) had been unable to obtain an outpatient appointment. The most common pathological finding in trauma cases was rib fracture in 40 (81.6%) patients. Tube thoracostomy was applied for 5 (10.2%) patients due to post-traumatic hemothorax or pneumothorax. Patients who presented to the emergency department were evaluated according to whether they were treated in the thoracic surgery service or were followed without hospitalization after being assessed in the emergency department. Accordingly, 22 (44.9%) of the 49 patients who presented with trauma were hospitalized. In comparison, 10 (16.1%) of the 62 patients who presented for non-traumatic reasons were hospitalized, and this result was statistically

significant (p=0.001). In March-June 2020, when the first wave of the COVID-19 pandemic was observed in Türkiye, 12 patients presented due to trauma and five patients due to non-traumatic reasons. In September-December 2020, when the second wave was seen, 17 patients presented due to trauma and 24 patients due to non-traumatic reasons. Fifty-three patients presented in July-August 2020 and January-March 2021, when restrictions were relaxed after the pandemic waves. Of the 53 patients who presented during those periods, 33 presented for non-traumatic reasons, and 20 presented due to trauma (p=0.054).

Discussion

COVID-19, triggered by infection with the human pathogenic coronavirus SARS-CoV-2, was first identified in China at the end of December 2019 and was declared a pandemic by the World Health Organization in March 2020 due to its global spread[3]. As of March 11, 2020, when the first case was seen in Türkiye, various restrictions began to be implemented here. As of March 21, 2020, for example, a curfew was imposed on citizens over the age of 65. Restrictions for the geriatric population continued until the effective introduction of COVID-19 vaccines. For this reason, there were some changes in the presentations of the geriatric population to the hospital during this period.

While it is to be expected that patients presenting to the emergency department due to thoracic trauma are mostly male, in our study, it was found that 29 (59.2%) female patients and 20 (40.8%) male patients applied to the emergency department due to thoracic trauma. Thus, women were more likely to apply to the emergency department with trauma numerically and proportionally. We think that the reason for this was the curfew that was in place during the pandemic period, with women working more at home with more active home lives. For non-traumatic thoracic surgery, 39 (62.9%) male patients and 23 (37.1%) female patients presented to the emergency services. Both numerically and proportionally, males were more likely to present to the emergency department for non-traumatic reasons. We think this is because men had more sedentary home lives than women throughout the pandemic restrictions.

Table 1 shows that the reasons among the geriatric population over the age of 80 for presenting to the hospital for thoracic surgery also changed moving forward from March 2020, when the pandemic started, to February-March 2021, when COVID-19 vaccines began to be administered effectively. Although admissions due to trauma and non-traumatic reasons were very rare at the beginning of the pandemic, emergency service applications increased in the following periods with the relaxation of restrictions and the start of COVID-19 vaccine administration. In a study conducted in Germany, although the average daily number of patients who presented to the hospital's emergency clinic was 131 as of February 2020, it decreased to 88 patients per day as of March 2020, at the start of the pandemic[4]. It was similarly observed that the number of patients presenting to the emergency department in the same clinic and requiring surgery secondary to trauma decreased considerably compared to the number of patients who required conservative treatment, and the authors stated that the reason for this was the curfew applied in Bavaria due to the pandemic[5].

Other researchers reported that although the number of hospital admissions due to injury decreased in the United States due to social distancing and other restrictions, the rate of penetrating traumas increased among all trauma cases[6,7]. In our study, as shown in Table 2, the number of patients presenting to the emergency services decreased during the major pandemic waves. The restrictions were designed for the segment of the population over 65 years of age.

In a study of 400 patients aged 65–100 years in which etiologies were evaluated for geriatric patients who presented to the emergency department due to trauma, it was found that 314 (78.5%) of the patients had presented after falling[8]. In our study, the etiological reason was falling for 44 (89.8%) of the 49 patients (89.8%) in the emergency department due to thoracic trauma in the first 12 months of the pandemic. Falling was the most common cause of trauma in the geriatric population during this period, in line with the literature. In a study conducted in England, 220000 applications were made to emergency services due to geriatric trauma between 2017 and 2018[9]. In our study, 49 (1.7%) of 2879 thoracic surgery consultations coming to our clinic from the emergency department during the pandemic were due to thoracic trauma in geriatric patients over the age of 80.

Rib fractures after chest trauma increase mortality in the geriatric population by two times compared to the younger population[10]. In our study, 40 of 49 patients who presented due to trauma had rib fractures. Other researchers found the mortality rate to be 20.1% in the geriatric population with rib fractures[10,11]. In our study, mortality was observed for 9 (22.5%) of the 40 patients who had rib fractures, and our data are consistent with the literature.

When we evaluated the hospitalization rates after admission to the emergency department, it was found that 22 (44.9%) trauma patients and 10 (16.1%) patients who presented with non-traumatic reasons were hospitalized in our clinic. We think that the most important reason for the low hospitalization rates of patients

Table 1. *Evaluation of demographic and clinical characteristics of the patients*

Variables		Thoracic trauma N	Thoracic trauma %	Non-traumatic reasons N	Non-traumatic reasons %	p-value
Gender	Male	20	40.8	39	62.9	0.021
	Female	29	59.2	23	37.1	
Age (year) (Mean ± StD)		85.65±4.56		85.32±4.71		0.711
CCI	0–7	33	67.3	36	58.1	0.317
	8–15	16	32.7	26	41.9	
CCI (Mean ± Std)		6.59±2.01		7.01±1.27		0.180
To the emergency room status after application	Discharge	27	55.1	52	83.9	0.001
	Admission	22	44.9	10	16.1	
Mortality	Yes	9	18.4	4	6.5	0.053
	No	40	81.6	58	93.5	

N: Number, CCI: Charlson Comorbidite Index, Std: Standart deviation.

Table 2. *Evaluation of patients' reasons for applying to the emergency department according to pandemic attacks*

Variables		Thoracic trauma N	Thoracic trauma %	Non-traumatic reasons N	Non-traumatic reasons %	p-value
Pandemic 1st attack application (March-June 2020)		12	24.5	5	8.1	0.054
Pandemic 2nd attack application (September-December 2020)		17	34.7	24	38.7	
Period after attacks (July-August 2020, January-March 2021)		20	40.8	33	53.2	
Causes of thoracic trauma	Fall	44	89.8			
	Traffic accident	4	8.2			
	Minting	1	2			
Causes of non-traumatic reasons	Pleural effusion			44	70.9	
	Other (lung abscess, pneumomediastinum, malignancy, pneumothorax, control)			18	29.1	
Symptoms of non-traumatic reasons	Dyspnea			48	77.4	
	Cough			4	6.5	
	General condition Disorder			5	8.1	
	Control			3	4.8	
	Hematemesis			1	1.6	
	Chest pain			1	1.6	

presenting for non-traumatic reasons is that our hospital is the largest pandemic hospital in Türkiye and Europe, and recommended hospitalizations for asymptomatic complaints are often refused by patients or their relatives due to fear of COVID-19 exposure.

Another study stated that rib fixation should not be applied to patients over 80 years of age because osteoporosis would not be successful in this age group due to osteoporosis[11]. In our study, rib fixation was not applied for patients over the age of 80 who had rib fractures, and conservative treatment was preferred.

When the literature is examined, a significant decrease is observed in outpatient and emergency service applications during the pandemic period[12,13]. In a study by Barten et al. [14] in the Netherlands in 2020 examining the emergency services of three hospitals not related to COVID-19, they reported a 66% decrease compared to 2019. In our study, when our patients' presentations to the emergency department for thoracic surgery were evaluated, it was seen that 5 (8.1%) patients presented in the first wave of the pandemic, 24 patients (38.7%) shown in the second wave, and 33 patients (53.2%) presented outside of those two periods. Although the pandemic continues, the number of trauma patients admitted to the emergency department has remained numerically proportional in every period. In contrast, presentations for non-traumatic reasons have increased gradually. We think the main points affecting this finding are that the vaccination program has begun, restrictions were reduced due to vaccinations, and the fear of contagion has been reduced by trust in vaccines.

Limitations of the Study

The main limitations of this study are its retrospective nature, the fact that it was conducted at a single center, the small number of patients due to the limited age range, and the inability to perform a long-term survey analysis due to the recent period being considered.

Conclusion

We know that the disease course of many patients, especially patients with malignancies, continues to progress with the frequent occurrence of chronic diseases or diseases with asymptomatic and progressive characteristics in the geriatric population. At the same time, pandemic restrictions may cause difficulties in reaching the hospital. For this reason, we advise that the geriatric population, especially older geriatric patients, not delay hospital visits in the face of any other pandemic-related restrictions that may be applied. The general public should also be made aware of this issue. Otherwise, the social inactivity imposed as a result of such pandemic-related restrictions may increase the mortality rate among geriatric patients due to chronic diseases or neoplasias far beyond the mortality rate that occurs due to the pandemic itself.

Ethics Committee Approval

Approval for this study was obtained from the local ethics committee (Date: 23.06.2021, No: E1-21-1864).

Conflict of Interest

The authors declare that there are no conflicts of interest.

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OLGU SUNUMU / *CASE REPORT*

Melanotic Neuroectodermal Tumor of Infancy: A Rare Case Report

İnfantil Melanotik Nöroektodermal Tümör: Nadir Bir Olgu Sunumu

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ABSTRACT

Melanotic neuroectodermal tumor of infancy (MNTI) is a rare, rapidly growing, and pigmented neoplasm of neural crest origin. It predominantly affects the maxilla of infants during the first year of life. A seven-month-old boy presented with a mass approximately 5 cm in diameter in the right oral cavity. On computerized tomography, a lytic expansile lesion was detected in the right maxilla. Microscopically, the tumor consisted of two different neoplastic cell proliferation, located peripherally and centrally, arranged in alveolar clusters within the fibrous connective tissue. Immunohistochemically, peripheral tumor cells showed diffuse staining for Pancytokeratin and HMB-45; the central cells were positive for CD56 and Synaptophysin. MNTI is a rare tumor that can be easily confused with malign small round cell tumors, especially in small biopsies. It has characteristic histomorphological and immunohistochemical findings. Its biological behavior is not fully understood. These tumors can present locally aggressive behavior and a high recurrence rate.

Key words: *melanin; neuroectoderm; infant; tumor*

ÖZET

İnfantil melanotik nöroektodermal tümör (IMNT), nöral krest kökenli, hızlı büyüyen, pigmente nadir bir neoplazmdır. Özellikle bebeklerde, yaşamın ilk yılında, maksillada ortaya çıkar. Yedi aylık erkek çocuk, oral kavitede yaklaşık 5 cm çapında kitle ile başvurdu. Bilgisayarlı tomografide, sağ maksillada ekspansil litik kitle saptandı. Mikroskopik olarak tümör, fibröz bağ dokusu içerisinde, alveolar kümeler şeklinde dizilim gösteren, periferal ve santral yerleşimli, iki farklı neoplastik hücre proliferasyonundan oluşmakta idi. İmmünohistokimyasal olarak periferal tümör hücreleri Pansitokeratin ve HMB-45 ile, merkezi tümör hücreleri CD56 ve Sinaptofizin ile immünopozitif ekspresyon gösterdi. IMNT, özellikle küçük biyopsilerde, malign küçük yuvarlak hücreli tümörler ile tanısal karışıklığa neden olabilen nadir bir tümördür. Karakteristik histomorfolojik ve immünohistokimyasal bulgulara sahiptir. Biyolojik davranışı henüz tam olarak anlaşılamamıştır. Bu tümörler lokal agresif davranış gösterebilir ve yüksek rekürrens oranlarına sahiptir.

Anahtar kelimeler: *melanin; nöroektoderm; infantil; tümör*

Introduction

Melanotic neuroectodermal tumor of infancy (MNTI) is a rare, rapidly growing, and pigmented neoplasm[1]. It was first described by Krompecher[2] in 1918. MNTI originates from the neural crest and comprises comparatively primitive pigment-producing cells. MNTI predominantly arises in the head and neck zone and most frequently involves the maxilla[3]. Various names have been used for this neoplasm because of the unknown cell origin and infrequent occurrence[4]. This report aimed to describe radiological, histopathological, and immunohistochemical features of a rare case of MNTI.

Case Report

A seven-month-old male child was applied to the Otolaryngology clinic with a mass in the right oral cavity for about a month. The mass was initially small but grew rapidly and arrived at the present size during the time. On computerized tomography of the head and neck, a lytic expansile lesion was detected in the right maxilla (Fig. 1a), which had intense homogeneous contrast (Fig. 1b). No other known notable findings existed. During the surgery, a tracheostomy was performed on the patient due to the oral mass. A solid tumor that filled the oral cavity exhibited infiltrative growth into the surrounding maxilla and base of the nose. The tumor was excised for subsequent pathological examination with a preliminary diagnosis of odontogenic myxoma. The defect repair in the maxillary bone was left to the second operation. Macroscopically, this mass was brownish, with well-circumscribed margins, measuring 5×4×2 cm in diameter (Fig. 1c), and had a heterogeneous grayish-black

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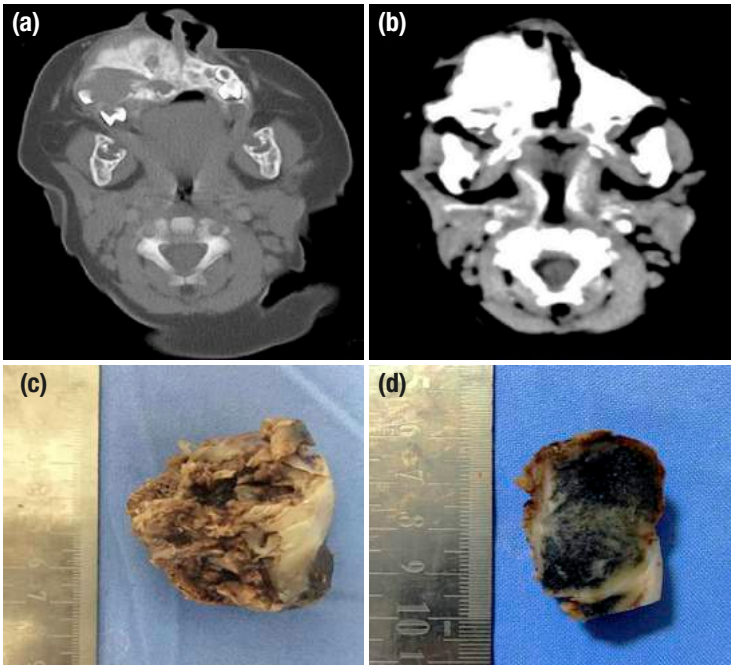

Figure 1. a–d. *Computed tomography (CT) showed an expansive mass measuring 5 × 4 × 3 cm that involved the middle of the anterior maxilla region with bone destruction, extending superiorly and medially* ***(a)****. Contrast-enhanced computed tomography showed a radiolucent osteolytic lesion expanding the surrounding bone* ***(b)****. Macroscopic specimen; a firm, brown-colored, well-demarcated mass* ***(c)****. The cut surface was colored black-gray* ***(d)****.*

appearance on cut sections (Fig. 1d). No foci of hemorrhage, necrosis, calcification, or areas of cystic change were observed. The tumor was microscopic from two distinct types of neoplastic cell proliferation arranged in alveolar nests and irregularly solid sheets within a densely sclerotic fibrous connective tissue stroma (Fig. 2a, 2b). The centrally located cells consisted of small, darkly stained cells with hyperchromatic nuclei and scant cytoplasm. The peripherally located cells were larger epithelioid cells that contained nuclei with vesicular nuclear chromatin and melanin pigment (Fig. 2c, 2d). Necrosis was not seen.

Immunohistochemically, although the peripheral tumor cells showed diffuse staining for HMB– 45 (Fig. 3a), Pancytokeratin (Fig. 3b), and FLI-1, the central cells were positive for NSE, Synaptophysin (Fig. 3c), CD56 (Fig. 3d), and FLI-1. Immunostains for S100, CD99, Melan A, and CD45 were consistently negative in tumor tissue. The final histopathological diagnosis was MNTI. The patient showed no recurrence or metastases in her latest follow-up exam in March 2021.

Discussion

MNTI is a rare, rapid-growing, and pigmented neoplasm arising in infants[4]. It has a mild male preference. MNTI commonly occurs in the first year of life[3]. It has been reported to occur in a small number of patients in older children and adults[5].

MNTI usually arises in the head and neck region. The most common regions are, respectively, the maxilla (68–80%), skull (10.8%), and mandible (5.8%). In our case, it was localized in the maxilla. It can also occur at the mediastinum, epididymis, testis, ovaries, extremities, and brain[7].

MNTI was first described by Krompecher[2] in 1918 as "Congenital melanocarcinoma." In 1966, Borella and Gorlin[8] suggested that these tumors are of neural crest origin because of the high level of vanillylmandelic acid (VMA) in urine, like other neuroectodermal tumors. Also, as these tumors are often seen in infancy, they suggested using the term MNTI[9,10]. Various names have been used in the past for this neoplasm, including "melanotic epithelial odontoma, congenital melanocarcinoma, melanotic progonoma, melanotic ameloblastoma, retinal anlage tumor, pigmented adamantinoma, congenital pigmented epulis, and melanocytoma." Usually, this neoplasm is associated with a rise in urinary VMA excretion, similar to another neuroectodermal neoplasm[6,7].

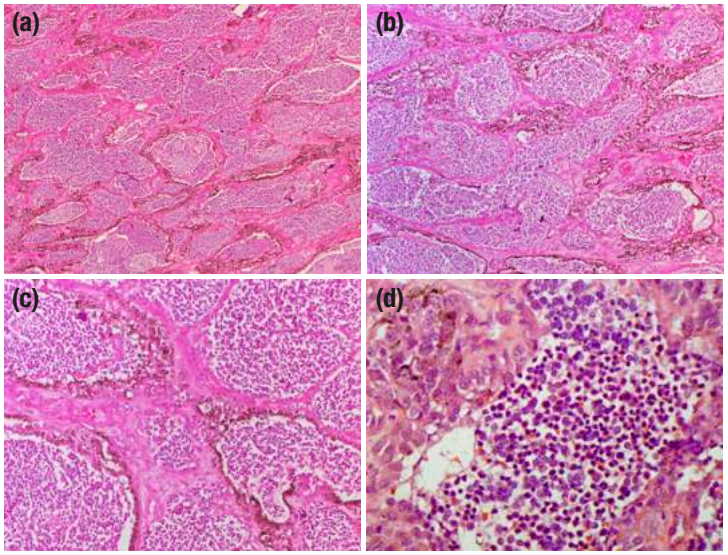

Figure 2. a–d. *Tumor cells are arranged in an alveolar pattern separated by fibrovascular stroma (H&E, 40×)* ***(a)****, (H&E, 100×)* ***(b)****. Biphasic tumor cell population, with large and small cells (H&E 200×)* ***(c)****. Two distinctive types of cells; small cells with scanty cytoplasm and hyperchromatic round nuclei, were seen in the center, and large epithelioid cells with abundant cytoplasm, round vesicular nucleus, and melanin pigment were seen in the periphery (H&E, 400×)* ***(d)****.*

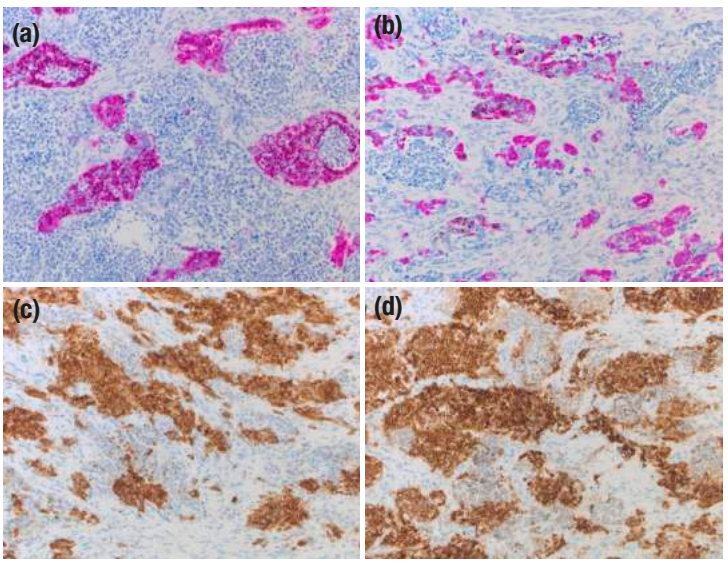

Figure 3. a–d. *Large epithelioid cells were positive for HBM-45* ***(a)*** *and PanCK* ***(b)****, and small cells were positive for Synaptophysin* ***(c)*** *and CD 56 (IHC, ×200)* ***(d)****.*

In the preoperative period, catecholamines such as VMA, noradrenaline, adrenaline, and neuron-specific enolase secreted by tumor cells support that the tumor is of neural crest origins such as pheochromocytoma and neuroblastoma. Following the surgery, these catecholamines are returned to normal levels[4,11].

Radiologically, the tumor introduces as a well-circumscribed radiolucent lytic lesion within the bone that may have features concerning local destruction. Computed tomography scans generally display a hyperdense tumor due to the presence of melanin and emphasize bone remodeling and expansion. Magnetic resonance imaging generally shows a demarcated, enhancing, and hypointense tumor on T1- and T2-weighted imaging[6,12].

Histomorphological findings show similar features in almost all MNTI cases published in the literature. Tumour includes two types of cells: one of them has

a small, less-differentiated, primitive appearance and scant cytoplasm, and the other one is a large epithelioid cell, which has a differentiated appearance, pale abundant cytoplasm, and includes melanin pigment. These characteristic cells are arranged in alveolar nests and solid sheets within a densely fibrous stroma. Mitoses or pleomorphism were not seen. The small cells were strongly positive for synaptophysin, an immunohistochemical marker supporting the neuroendocrine features of this tumor. Staining of the larger cells with pan-cytokeratin and HMB-45 supported epithelial differentiation and features seen with melanocytic differentiation[13]. Also, in our case, expression was observed in both cell populations for FLI-1.

The differential diagnosis of MNTI contains other small round blue cell neoplasms of infants, particularly neuroblastoma, Ewing sarcoma, alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, and lymphoma. Also, melanogenic tumors of soft tissue should be considered in different diagnoses. It can be difficult to distinguish MNTI from other neuroendocrine tumors such as neuroblastoma, especially in small biopsy specimens. Typical features of MNTI, such as the biphasic population of epithelioid and primitive neurogenic cells, its characteristic immunohistochemical findings, and the clinical symptoms, can help distinguish it from other neoplasms[5,6].

Although MNTI cases are generally considered benign, their biological behavior is not fully understood. These tumors grow rapidly and present locally aggressive behavior and a high recurrence rate. It has been reported that cases show more aggressive behavior in tumors, where the small cell component is dominant, and the large cell component is not evident. However, there are no established criteria for distinguishing benign from malignant lesions[3]. The treatment option is generally surgical excision, as it was in the present case. In the literature, some studies point out that there is no difference between curettage and resection in recurrence rate[4]. In cases where accurate surgical eradication is not possible, radiotherapy and chemotherapy are potential alternative treatments. However, this is controversial[6,13].

Conclusion

MNTI is a rare tumor that can be easily confused with malign small round cell tumors, especially in small biopsies. Characteristic histomorphological and immunohistochemical findings are useful in the differential diagnosis. Knowing MNTI can prevent unnecessary preoperative and radical surgical treatments. These patients need to be followed up closely due to locally aggressive behavior and high recurrence rates.

Conflict of Interest

There are no conflicts of interest.

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DERLEME / *REVIEW*

The Effect of Back Massage on Sleep Quality: A Systematic Review

Sırt Masajının Uyku Kalitesi Üzerine Etkisi: Sistematik Bir İnceleme

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ABSTRACT

Aim: *The conditions such as pregnancy, old age, health problems and hospitalization negatively affect the sleep quality. Improving patients' sleep problems is a part of nursing care. Nurses try to reduce patients' sleep problems by using back massage, which is one of the non-drug methods. This systematic review was carried out to evaluate the effect of back massage application on the sleep quality of individuals.*

Material and Method: *The PRISMA protocol was followed in the conduct of the study. MEDLINE (EBSCOhost), SAGE, SCIENCE DIRECT, ULAKBIM (national academic network and information center), COCHRANE databases, and SEMANTIC SCHOLAR search engine were scanned through Atatürk University's internet access network. The literature review conducted using Turkish and English keywords, 1044 articles were reached, and 14 articles met the inclusion criteria. Prospective, randomized controlled, or experimental/quasi-experimental design research articles written in Turkish and English were included in the review.*

Results: *71.4% of the reviewed studies had randomized control groups. In 92.8% of the studies, it was determined that the massage duration varied between 3 and 30 minutes and that the back massage improved sleep quality.*

Conclusion: *In this systematic review, it was concluded that back massage application was an effective intervention in increasing the sleep quality of the patients and that this massage should be applied for at least 10 minutes late in the day and every session.*

Key words: *back massage; sleep; nursing; systematic review*

ÖZET

Amaç: *Hamilelik, yaşlılık, sağlık sorunları ve hastaneye yatış gibi durumlar uyku kalitesini olumsuz etkiler. Hastaların uyku problemlerini iyileştirmek hemşirelik bakımının bir parçasıdır. Hemşireler ilaç dışı yöntemlerden biri olan sırt masajı yaparak hastaların uyku problemlerini azaltmaya çalışırlar. Bu sistematik derleme, sırt masajı uygulamasının bireylerin uyku kalitesine etkisini değerlendirmek amacıyla yapılmıştır.*

Materyal ve Metot: *Çalışma PRISMA protokolü takip edilerek yürütülmüştür. Atatürk Üniversitesi internet erişim ağı üzerinden MEDLINE (EBSCOhost), SAGE, SCIENCE DIRECT, ULAKBİM (ulusal akademik ağ ve bilgi merkezi), COCHRANE veri tabanları ve SEMANTIC SCHOLAR arama motoru taranmıştır. Türkçe ve İngilizce anahtar kelimeler kullanılarak yapılan literatür taramasında 1044 makaleye ulaşılmış ve dahil edilme kriterlerine uyan 14 makale incelenmiştir. İncelemeye Türkçe ve İngilizce olarak yazılmış prospektif, randomize kontrollü veya deneysel/yarı deneysel tasarımlı araştırma makaleleri alınmıştır.*

Bulgular: *İncelenen araştırmaların %71,4'ü randomize kontrol grupludur. Çalışmaların %92,8'inde masaj süresinin 3 ile 30 dakika arasında değiştiği ve sırt masajının uyku kalitesini iyileştirdiği belirlenmiştir.*

Sonuç: *Bu kapsam incelemesinde sırt masajı uygulamasının hastaların uyku kalitesini artırmada etkili bir müdahale olduğu ve bu masajın günün geç saatlerinde ve her seansta en az 10 dakika uygulanması gerektiği sonucuna varılmıştır.*

Anahtar kelimeler: *sırt masajı; uyku; hemşirelik; sistematik inceleme*

Introduction

Sleep is one of the life activities with physiological, psychological, and social dimensions. Sleep, which is usually repeated every 24 hours and has an average daily duration of 6–8 hours in adults, is a cyclical process that relieves individuals by removing them from stress and responsibilities and provides energy storage again from spiritual and physical aspects. Individual factors such as age, diet, general health status, presence of pain, drugs used, pregnancy and birth processes, and environmental factors such as ambient temperature, noise, and features of the bed used may affect the sleep process[1–3]. Hospitalization is one of the conditions that

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negatively affect the sleep process. The studies indicated that hospitalized patients' sleep quality was impaired, and they had sleep problems[4–8].

Impairment in sleep quality is characterized by the symptoms such as spending too much time for transition to sleep, shortening sleep duration, unrest during the night, continuous movement during sleep, and waking up without feeling rested. Low sleep quality causes fatigue, deterioration in concentration, learning disability, nervousness, increased sensitivity to pain, hallucinations, slowing of growth, weakening of the immune system, susceptibility to infections, delay in wound healing, decrease in quality of life, and increased risk of mortality and morbidity [3,9]. Pharmacological agents are frequently used to overcome sleep problems. However, the pharmacological agents used may cause undesirable effects and economically require additional expenditure. Nurses are responsible for identifying the sleep process in hospitalized patients, determining the changes in sleep patterns due to disease, and establishing a healthy sleep pattern with appropriate interventions[3,8–10]. One of the non-pharmacological interventions proposed to improve sleep quality and facilitate sleep is applying the massage. Massage is a systematic touch to the body to reduce tension, provide relaxation, and stimulate and accelerate blood circulation[11,12]. Massage decreases fatigue, exhaustion, tension, and pain by showing a sedative effect and improves the feeling of trust in individuals. Studies indicated that massage relieves pain and fatigue, reduces blood pressure, decreases heart rate, decreases cortisol release and depression, and regulates sleep[11,13–27]. Therefore, massage is a method that is frequently used to overcome sleep problems. Massage application is also a subject of nursing research since it is included in the Nursing Interventions Classification System with code 1480[28].

This review provided an overview of the studies conducted to investigate the effect of back massage on sleep quality.

The research questions in the study are as follows:

Question 1: What is the distribution of studies according to the patient group in the sample?

Question 2: What is the distribution of the back massage applied in studies according to its duration?

Question 3: What is the distribution of disciplines applying back massage in studies?

Question 4: What is the distribution of the effectiveness of back massage in studies?

Methods

Protocol

The review follows the systematic methodology outlined by Liberati et al. 29. Consistent with this methodology; the review was conducted in 5 steps. Step 1 involved developing the research questions; Step 2 identifying relevant studies; Step 3 selecting studies; Step 4 charting data; and Step 5 collating, summarizing, and reporting results. The PRISMA checklist for systematic reviews was used in the reporting29.

Search Strategy

At first, a literature review was conducted to determine the keywords. It was decided that the Turkish keywords would be "sirt masaji, uyku, hemşirelik, randomize," and English keywords would be "back massage, sleep, nursing, randomized". MEDLINE (EBSCOhost), SAGE, SCIENCE DIRECT, ULAKBIM (national academic network and information center), COCHRANE databases, and SEMANTIC SCHOLAR search engine were scanned between 26–30 November 2018 through Atatürk University's internet access network, by using those keywords. No restriction was made on the publication date of the studies.

Inclusion Criteria

The research articles with prospective, randomized controlled or experimental/quasi-experimental design written in Turkish and English, evaluating the effect of back massage application with a sleep quality scale or patient statements, and published as full text were included in the review.

Exclusion Criteria

Descriptive or retrospective studies, research designs in the form of thesis, book, book chapter, review, letter to the editor, case and reports, and the studies including the massage applications performed in babies were not included in the review.

Study Selection

The literature review was first carried out in five databases, a search engine in the first step, and all full-text articles obtained were combined (n=1044). A data coding form was created, and all articles were coded and transferred to this form. All authors independently reviewed the titles and abstracts of the articles. Repeated articles were determined and deleted (n=82). Among the articles obtained (n=962), the articles that did not have the inclusion criteria (n=602) and were not related to the subject (n=342)

were excluded. Among the remaining articles (n=18), the articles that were not in English or Turkish (n=3) and the article including the massage application in babies (n=1) were determined and excluded. As a result, 14 articles were included in the review [11,13,16–27].

The researchers independently evaluated the research regarding purpose, method, sample characteristics, and applied intervention. They scored the appropriate item as one and the unsuitable item as 0. For the research that scored 4 points from one of the researchers and below four from the other, the third researcher's score determined the decision. The flow chart is presented in Figure 1.

Analysis of the Results

Data were grouped according to the determined research questions and evaluated in frequency and percentage.

Results

This systematic review included the results of the articles investigating the effect of back massage on sleep quality.

Years and countries: While the first evidence in the relevant full texts on the subject reached includes the results of the studies conducted in 1992, the most recent evidence published belongs to the results of the studies conducted in 2017 (1992-1, 1998-1, 2009-1, 2010-3, 2012-1, 2014-2, 2015-1, 2016-2, 2017-2). The studies included in the review appeared mainly conducted in the USA and India (USA 4, India 4, Türkiye 3, Brazil 1, Taiwan 1, Iran 1).

***Research type*:** 10 of 14 studies (71.4%) were randomized controlled trials. Four studies had a non-randomized/quasi-experimental design and no control group.

***Individuals included in the sample*:** It was determined that adult patients diagnosed with cardiovascular disease (n=5), cancer patients (n=2), children and adolescents with psychiatric disorders (n=1), postpartum women (n=1), patients with dementia (n=1), caregivers of cancer patients (n=1), patients undergoing hemodialysis (n=1), intensive care patients (n=1) and elderly people living in nursing homes (n=1) were included in the studies. The individuals included in the studies were between 7 and 80 years.

***Sample size*:** While the sample size of the studies ranged from 30 and 74 people, the control group size of the great majority of them was 30 or below 30.

***Those who applied back massage and the duration of back massage*:** Back massage was applied by the students from the psychology department (n=1), massage therapist (n=2), physiotherapist (n=1), and nurse (71.4%, n=10) within a maximum of 4 weeks with light/medium pressure for a maximum of 30 minutes, including at least 3

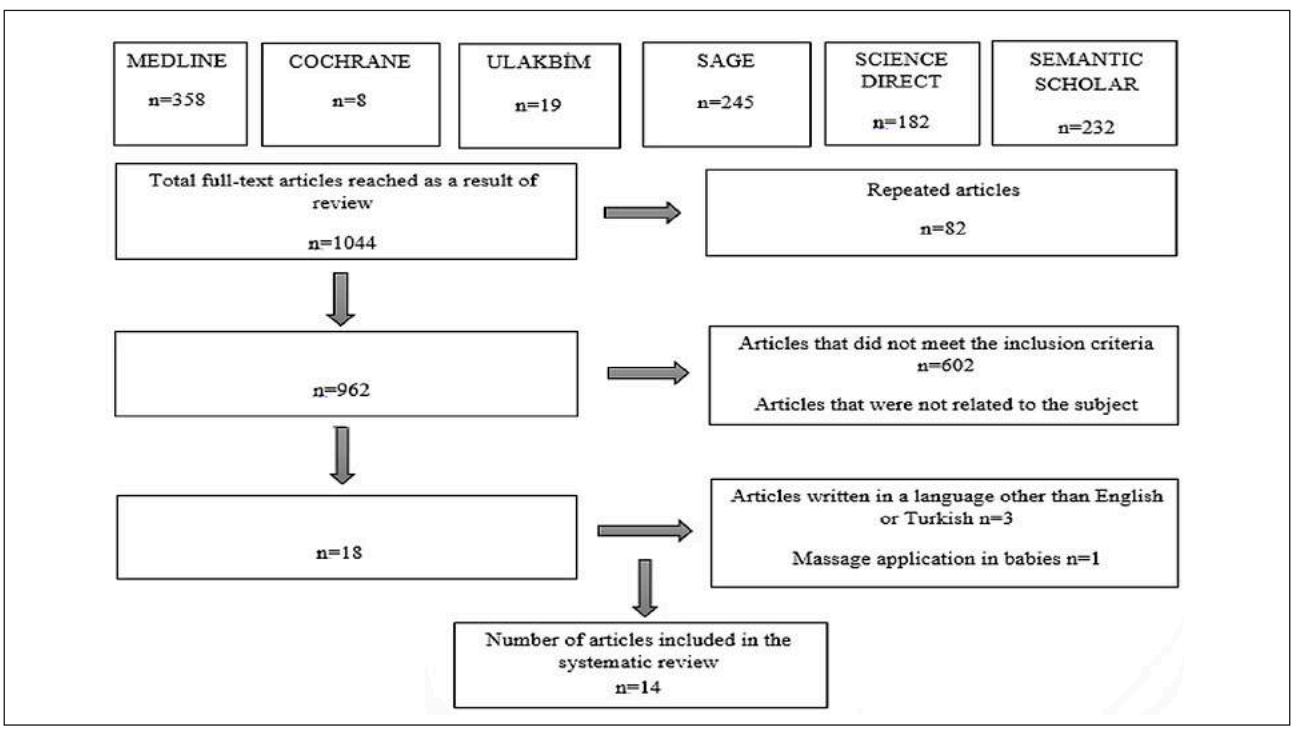

Figure 1. *Flow chart.*

minutes for a session, with the combinations of effleurage, petrisage, friction, and tapotement maneuver.

***The effect of back massage on sleep*:** All studies included in the review (92.8%), except for one, determined that back massage shortened the duration of falling asleep, increased sleep duration, and improved sleep quality by reducing sleep disorders.

The features of the articles are presented in Table 1.

Discussion

This study aims to evaluate the effect of back massage on sleep quality; 14 articles meeting the inclusion criteria were reached[11,13,16–27]. The fact that most of the studies were carried out in the countries in Asia and generally in the last decade suggests that the interest in non-pharmacological methods has increased in these regions in recent years. The fact that 10 of these studies (71.4%)[11,13,17–19,22,24–27] had a randomized controlled research design suggests that the results obtained had high evidence. The other four studies[16,20,21,23] had a lower level of evidence with a non-randomized pretest-posttest quasi-experimental research design. The fact that the individuals discussed in the articles included in this systematic review are in a wide age range and vary greatly in terms of disease indicates that many diseases may affect the sleep quality of individuals in all age groups. In most of the studies examined in this review, the sample size is limited to the parametric test. It is considered that large sample studies are needed for more reliable results. In the studies included in the review, while the time of back massage application was not indicated in some studies, it was observed that they were usually applied during the evening hours and at night before going to bed[11,16,17,19–21,25,26]. The results show that the back massage applied late in the day effectively improves sleep quality. This result is also consistent with the circadian rhythm. It is thought that there is a need for studies evaluating the effect of massage applied earlier. The application time of back massage appeared to vary in the studies. While the massage session duration was not indicated in one of the studies[19], the total duration of massage was not shown due to continued application from patients' admission to discharge in study[21]. In other studies included in the review, the back massage was applied in a session for 3–30 minutes, and that light and medium pressure were applied during the massage. In the study of Harris et al., in which light pressure was applied, and the session duration was the shortest by 3 minutes[11], it was found that back massage did not improve sleep quality. In other studies, it appeared that back massage is effective in improving sleep quality regardless of the duration of application. Nevertheless, when the studies were analyzed in terms of statistical significance values, it appeared that the massage session duration was at least 10 minutes in the studies indicating the values p£0.001 and z >1.96. These results suggest that it will be more appropriate to plan the session duration of back massage for at least 10 minutes. In the studies included in the review, it appeared that back massage was mostly applied (71.4%) by nurses[11,13,16–18,20–22,26,27], however, it is seen that massage therapists[23,25] physiotherapist[19] and psychology students[24] applied back massage in a fewer number of studies. To assist the individuals in all life activities, they need a holistic approach, which is one of the nurses' responsibilities. The fact that nurses are further focused on the studies on sleep problems than other health professions can be explained by this approach and the responsibilities of nurses. Furthermore, massage applications are among the nursing interventions and are considered a part of nursing care. In 13 (92.8%) of the studies included in the review, it was determined that there was a statistically significant difference between back massage and sleep and that back massage was effective in improving sleep quality; however, only in study[11], it was determined that there was no statistically significant relationship between back massage and sleep. It can be considered that the relevant therapeutic effect of back massage decreases cortisol, norepinephrine, and epinephrine levels by stimulating the sympathetic nervous system and thus improves the sleep quality of patients due to the physical and psychological relief it provides.

Ensuring high-quality individual/patient-centered and evidence-based care requires the implementation of appropriate, acceptable, safe, and effective nursing interventions[28]. Back massage, as a part of basic nursing care, may be useful in preventing polypharmacy since it decreases the consumption of sleeping pills, increases patient comfort, reduces costs, and improves sleep quality. So, nurses can provide an effective, economical, invasive, and non-pharmacological, complementary contribution to increasing the sleep quality of patients with sleep problems. They can also increase patient satisfaction by improving the quality of nursing care.

Conclusion

In this systematic review, it was determined that the health professional who mostly applied the back massage to improve patients' sleep quality was the nurse and that the back massage application positively affected the sleep quality of patients. Although there was no common view for the duration of back massage, it was

Table 1. *Features of the articles included in the review*

Authors, country of research	Research type	Sample	Groups	Intervention	Conclusion
1. Field et al. 1992; USA	Randomized controlled	Children and adolescents with psychiatric disorders aged between 7–18 years	n=20 control group n=52 experimental group	Medium-pressure back massage was applied by psychology students for 30 minutes per day every afternoon for 5 days. Night sleep was recorded as video.	The sleep duration of the group received back massage for a five-day period significantly increased and the time spent awake in bed decreased (p=0.01).
2. Richards, 1998; USA	Randomized controlled	Elderly male patients with a diagnosis of cardiovascular disease hospitalized in the intensive care unit of the hospital	n=24 control group n=17 experimental group	6 minutes of back massage was applied by the nurse.	The patients who received back massage slept more (more than 1 hour) than the control group, and the difference was found significant.
3. Pruthi et al., 2009; USA	Quasi-experimental	Patients diagnosed with breast cancer	n=35 (no control group)	Back massage was applied by massage therapist for 20 minutes using mineral oil.	Massage therapy was found to be effective in improving sleep quality (p<0.05).
4. Nerbass et al., 2010; Brazil	Randomized controlled	Patients aged between 40–80 years undergoing coronary artery bypass graft surgery	n=20 control group n=20 experimental group	Back massage was applied by the physiotherapist 2–3 hours before sleep (at 19.00) for 3 nights.	Massage therapy was found to be effective in improving sleep quality during recovery period after the CABG surgery (p=0.019).
5. Ko and Lee, 2010; Taiwan	Randomized controlled	Postpartum women aged 20 and over	n=30 control group n=30 experimental group	Back massage was applied by a certified massage therapist for 20 minutes using body lotion, once a day between the evening hours of 17.00–21.00 during 5 consecutive days.	It was observed that back massage application significantly improved the sleep disorder in postpartum women with sleep disorders (p<0.001).
6. Harris and Richards 2010; USA	Randomized controlled	Patients with dementia aged 65 years and older with sleep disorders	n=20 control group n=20 experimental group	3-minute low-pressure, slow, circular stroke back massage was applied by a certified geriatric nurse before going to bed for 2 nights.	No significant difference was observed in sleep improvement between the intervention group and control groups (p>0.05).
7. Cinar and Eser, 2012; Türkiye	Quasi-experimental	Elderly people living in nursing home	n=33 (no control group)	The group was given a 10-minute back massage daily with non-aromatic baby oil before going to bed for the first 3 days by a nurse researcher.	Massage was found to be effective in improving sleep quality (p=0.000).
8. Shinde and Anjum, 2014; India	Pretest-posttest randomized controlled	Intensive care patients (aged between 25–70 years)	n=30 control group n=30 experimental group	10–12-minute low pressure back massage was applied by the nurse researcher in the evening hours between 20.00–21.00 for three consecutive days.	Back massage was found to be significantly effective in improving sleep quality (p<0.05).
9. Mathpati and Dias, 2014; India	Pretest-posttest non-randomized control group	Patients with congestive heart failure (male patients aged between 35–65 years)	n=50 (no control group)	10 minutes of back massage was applied by the nurse using effleurage, petrisage, friction and tapotement maneuvers before going to bed for three consecutive days.	It was found that back massage significantly improved the sleep disorder in patients with congestive heart failure (z=3.76, >1.96).
10. Pinar and Afsar, 2015; Türkiye	Randomized controlled trial	Caregivers of cancer patients were studied	n=22 control group n=22 experimental group	15 minutes of medium pressure back massage was applied by the nurse researcher using effleurage, petrisage, friction and tapotement maneuvers with non-aromatic baby oil between the evening hours 17.00 and 20.00 for one week.	Back massage application was found to be significantly effective in improving sleep quality (p<0.001).
11. Unal and Akpinar, 2016; Türkiye	Randomized controlled	Patients aged between 18 and 60 years undergoing hemodialysis twice a week in the dialysis center	n=37 control group n=37 experimental group	30 minutes of back massage was applied by the nurse researcher using effleurage, petrisage, friction and tapotement maneuvers with baby oil for 2 days a week within 4 weeks.	Back massage was found effective in improving sleep quality (p<0.05).
12. Joys and Kumari, 2016; India	Pretest-posttest randomized controlled	Cardiothoracic intensive care unit	n=20 control group n=20 experimental group	20 minutes of back massage was applied by the nurse between postoperative days 2 and 5.	Back massage was found to be effective in improving sleep quality among postoperative patients after cardiac surgery (p<0.05).
13. Miladinia et al., 2017; Iran	Randomized controlled	Patients with acute leukemia receiving chemotherapy (aged between 18–50 years)	n=30 control group n=30 experimental group	After chemotherapy, 10 minutes of low pressure back massage with vaseline was applied to the patients by oncology nurse 3 times a week within 4 weeks.	It was determined that back massage significantly improved sleep quality in patients receiving chemotherapy for acute leukemia compared to the control group (p=0.003).
14. Sable et al., 2017; India	Pretest-posttest quasi-experimental	Adult patients with congestive heart failure	n=30 (no control group)	20 minutes of back massage was applied to the patients by the nurse researcher using effleurage, petrisage, friction and tapotement maneuvers 3 times in a day at 08.00 in the morning, 15.00 and 20.00 in the evening, every day from the first day of their admission to discharge.	Back massage has a significant effect in improving sleep duration and sleep quality (p£ 0.0001).

Articles are listed by the year of publication.

concluded that the massage should be applied late in the day and every session for at least 10 minutes. In line with these results, for the back massage procedure, it is recommended to conduct more studies with a larger number of samples and systematic review and meta-analysis for precise information.

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Conflict of Interest

No conflict of interest between authors

Ethical Approval

All necessary ethical permissions have been obtained

Authors' Contributions

RBA contributed to the study design; GA and EA searched the literature and performed data selection and extraction; RBA, GA, and EA analyzed the data and interpretation of results; RBA contributed to the critical debate; RBA, GA, and EA have read and approved the latest article.

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