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Abood S: Quality improvement initiative in nursing homes: the ANA acts in an advisory role. *Am J Nurs [Webcast]*. 2002 Jun [citation 12.08.2002]; 102 (6). Access: <http://www.nursingworld.org/AJN/2002/june/Wawatch.htm> PMID: 12394070.

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Prosnostic Significance of Prognostic Nutrition Index in Metastatic Renal Cell Carcinoma Patients Treated with Tyrosine Kinase Inhibitors

Tirozin Kinaz İnhibitörleri ile Tedavi Edilen Metastatik Renal Hücreli Karsinom Hastalarında Prognostik Nütrisyonel İndeksin Prognostik Önemi

Seher Yıldız TACAR, Mesut YILMAZ, İlkey GÜLTÜRK, Deniz TURAL

İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Turkey

ABSTRACT

Aim: The purpose of this study was to investigate the prognostic role of pretreatment Prognostic Nutritional Index (PNI) in metastatic renal cell carcinoma (mRCC) patients given pazopanib or sunitinib as first-line targeted therapy.

Materials and Methods: We retrospectively analyzed the treatment modalities, demographic, clinical, and pathological features of 77 patients with mRCC, and calculated prognostic nutritional index. Based on the median value, patients were grouped as those having low and high PNI values. The Kaplan-Meier method was used for survival analysis, and Cox-regression analysis was used for univariate and multivariate analyses.

Results: The overall median progression-free survival (PFS) and overall survival (OS) time for all patients were 15 months [95% confidence interval (CI): 10.9-19.1 months] and 27 months (95% CI: 15.9-38.1 months), respectively. Patients with low PNI had significantly shorter median PFS (11 vs 20 months, $p=0.001$) and OS (17 vs 40 months, $p=0.001$) than those with high PNI. In multivariate analysis, PNI was shown as an independent predictor on both OS and PFS. Moreover, Eastern Cooperative Oncology Group-Performance Status was shown as an independent predictor for OS and International Metastatic Renal-Cell Carcinoma Database Consortium-score for PFS.

Conclusion: Low PNI could be a significant prognostic marker for survival in mRCC patients who have received tyrosine kinase inhibitors as first-line target therapy.

Keywords: Metastatic, renal cell carcinoma, prognosis, PNI

ÖZ

Amaç: Bu çalışmada; birinci basamak hedefli tedavi olarak pazopanib veya sunitinib alan metastatik renal hücreli kanser (mRCC) hastalarında tedavi öncesi Prognostik Nütrisyonel İndeksi'nin (PNI) prognostik rolünü değerlendirmeyi amaçladık.

Gereç ve Yöntem: mRCC'li 77 hastanın tedavi modaliteleri, demografik, klinik ve patolojik özellikleri geriye dönük olarak incelendi ve PNI hesaplandı. Ortanca değere göre hastalar düşük ve yüksek prognostik nütrisyonel indeks gruplarına ayrıldılar. Sağkalım analizi için Kaplan-Meier yöntemi, tek değişkenli ve çok değişkenli analiz için Cox-regresyon analizi kullanıldı.

Bulgular: Tüm hastalar için genel medyan progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) süresi sırasıyla 15 ay [%95 güven aralığı (GA): 10,9-19,1 ay] ve 27 ay (%95 GA: 15,9-38,1 ay) olarak saptandı. Düşük PNI'si olan hastalarda, yüksek PNI'si olan hastalara göre anlamlı olarak daha kısa medyan PFS (11'e karşı 20 ay, $p=0,001$) ve OS (17'ye karşı 40 ay, $p=0,001$) saptandı. Çok değişkenli analizde PNI, hem OS hem de PFS üzerinde bağımsız bir öngörücü olarak gösterildi, ayrıca Eastern Cooperative Oncology Group-Performance Status OS için bağımsız bir öngörücü iken, International Metastatic RCC Database Consortium skoru ise PFS için bağımsız bir öngörücü belirteç olarak gösterildi.

Sonuç: Düşük PNI, birinci basamak tedavi olarak tirozin kinaz inhibitörleri alan mRCC hastalarında sağkalım için önemli bir öngörücü belirteç olabilir.

Anahtar Kelimeler: Metastatik, renal hücreli karsinom, prognoz, PNI

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INTRODUCTION

Renal cell carcinoma (RCC) is the 6th most common cancer in men and the 8th most common cancer in women, accounting for 2% to 3% of all adult cancers^{1,2}. Most patients are at the stage of localized disease at the time of diagnosis and are cured with surgery, but approximately 30% of patients present local or distant recurrence after nephrectomy³.

Despite therapeutic alternatives such as targeted therapies and immunotherapy, overall survival (OS) rates in metastatic RCC patients remain poor⁴. There are a number of prognostic indicators that influence a patient's therapy response and survival. Previous studies have revealed the usefulness of prognostic markers such as pathological stage, tumor grade, tumor subtype, sarcomatoid characteristic, tumor necrosis, and microvascular invasion^{5,6}.

Onodera et al.⁷ designed the Prognostic Nutritional Index (PNI), which is a simple index based on albumin and lymphocyte count. It has been shown that lower PNI values are associated with shorter survival. This relationship between survival and PNI has also been investigated in cancers such as breast, colorectal and lung cancers⁸⁻¹⁰.

There are limited number of studies evaluating the relationship between PNI and survival in RCC patients¹¹⁻¹⁴. In our study, we evaluated the prognostic effect of pre-treatment PNI value on survival in metastatic renal cell carcinoma (mRCC) patients receiving tyrosine kinase inhibitor (TKI).

MATERIALS AND METHODS

Patients

We examined patients diagnosed with mRCC, who were treated with targeted treatment (pazopanib or sunitinib) between August 2013 and September 2021. A total of 90 individuals with mRCC were retrospectively studied, including 74 patients having sufficient data.

This study involved mRCC patients receiving pazopanib or sunitinib as first-line therapy with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0.1 and 2. serum albumin levels and lymphocyte counts were recorded within one week before the treatment. Patients who did not comply with the above criteria or who had unstable or severe cardiac disease, uncontrolled brain metastases, concurrent malignancies and incomplete data files were excluded from the study.

Data Collection

The treatment methods, epidemiological, pathological, and clinical aspects of patients, and laboratory data of these patients were all searched retrospectively from the hospital

database. The variables that were recorded were baseline hemoglobin, neutrophil, platelet (PLT) counts, calcium, albumin, ECOG PS, time to systemic treatment, and date of death or last follow-up. PNI was calculated using the albumin value and total lymphocyte count [The formula of PNI: $0.005 \times \text{total lymphocyte count (mm}^3\text{)} + 10 \times \text{serum albumin value (g/dL)}$]. Different cut-off values for PNI were employed in the study examining the prognostic efficacy of PNI in mRCC, while median values were used in certain studies. It fluctuates from 41 and 51^{10,13,14}. We also used median values in our study. The patients were grouped according to the median value, as low PNI (PNI <48.25) and high PNI (PNI $\geq$ 48.25).

Statistical Analysis

Percentages were used to represent categorical variables. The mean and standard deviation of continuous variables were calculated (median and range). The chi-square test or Fisher's exact test were used to assess categorical variables.

OS and progression-free survival (PFS) were estimated using the Kaplan-Meier method and difference in survival was calculated using the log-rank test. The prognostic significance of clinical characteristics such as age, gender, history of cytokine and surgical treatment, pathology, number of metastatic locations, PFS, and OS was estimated using the Cox's proportional hazard model with a two-sided 95 percent confidence interval (CI). A p-value of 0.05 was considered as statistically significant. IBM Statistical Package for the Social Sciences Statistics version 23.0 was used to evaluate the clinical data.

RESULTS

Clinicopathological characteristics of patients are shown in Table 1. The median patient age was 64 (minimum: 37-maximum: 91) years. Of the 77 patients, 57 (76%) were male and 20 (23%) were female. The median PNI value was 48.25 (18-52). In the high PNI group, the rate of patients with a favorable International Metastatic RCC Database Consortium (IMDC) score (30.8%) was higher, while in the low PNI group, the rate of patients with a poor IMDC score (39.5%) was significantly higher (p=0.019). In the low PNI group, the central nervous system metastasis was seen at the rate of 17.6% while it was found to be 2.6% in the high PNI group. This difference was found to be statistically significant (p=0.028).

Survival Analysis

The median of OS and PFS for all patients was 27 months (95% CI 15.9-38.1 months) and 15 months (95% CI 10.9-19.1 months), respectively (Figure 1). The median OS was 17 months (95% CI, 7.8-20.2 months) in the low PNI group, and the median OS was 40 months (95% CI, 25.9-54.1 months) in the high PNI group (log-rank p=0.001) (Figure 2).

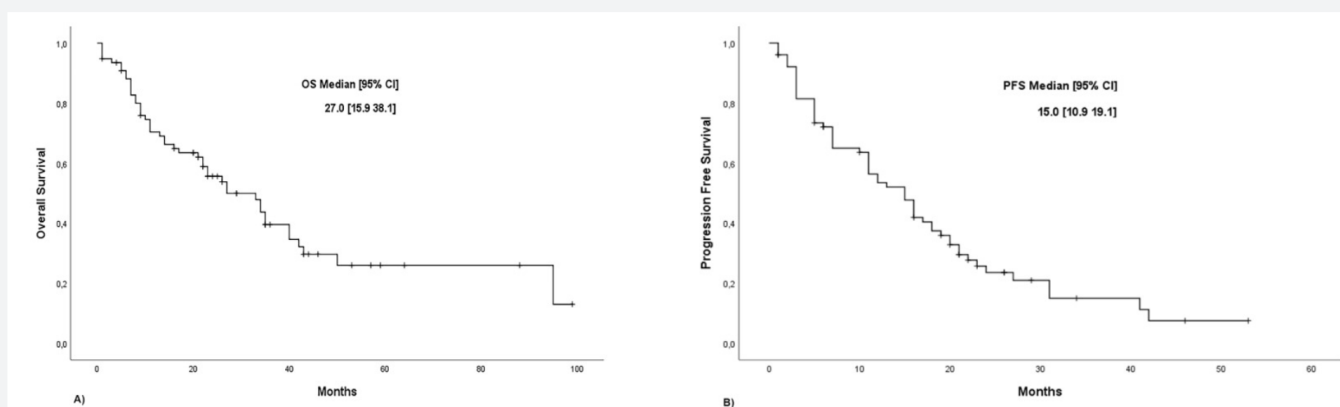


Figure 1. Kaplan-Meier curves showing (A) overall survival and (B) progression-free survival in all the patients

While the median PFS was 11 months (95% CI, 7.7-14.3 months) in those with low PNI, the median PFS was 20 months (95% CI, 16.6-23.4 months) in those with high PNI (log-rank $p=0.001$). Those with low PNI had significantly shorter OS and PFS compared to the high PNI group (Figure 2).

The median OS was 95 months (95% CI, 7.1-182.9 months), 33 months (95% CI, 21.2-44.8 months), and 14 months (95% CI, 21.2-44.8 months) in those with favorable, intermediate, and poor IMDC scores, respectively (log-rank, $p=0.104$). Similar results were observed in PFS. Although there was a numerical difference between the groups, the difference was not significant due to the small number of patients (Figure 3).

Table 2 shows a Cox regression analysis of factors that may be predictive for PFS. PNI and IMDC risk status had a significant

effect on PFS in univariate Cox regression analysis. In a multivariate Stepwise Cox regression analysis, those with poor PNI had statistically significantly shorter PFS [hazard ratio (HR): 2.12, 95% CI 1.17-3.83, $p=0.013$]. Patients with IMDC poor-risk had a significantly shorter PFS than patients with favorable risk (HR: 2.12 95% CI: 1.17-3.83, $p=0.013$).

Table 3 shows a Cox regression analysis of factors that may be predictive for OS. In univariate Cox regression analysis, a significant effect of ECOG, PNI, and IMDC status on OS was observed. In multivariate Stepwise Cox regression analysis, shorter OS was observed in those with low PNI (HR: 2.68, 95% CI: 1.45-4.9, $p=0.002$), and longer OS was observed in those with ECOG-PS 0 and 1 compared to those with ECOG-PS 2 (HR: 0.22 95% CI: 0.08-0.6, $p=0.002$).

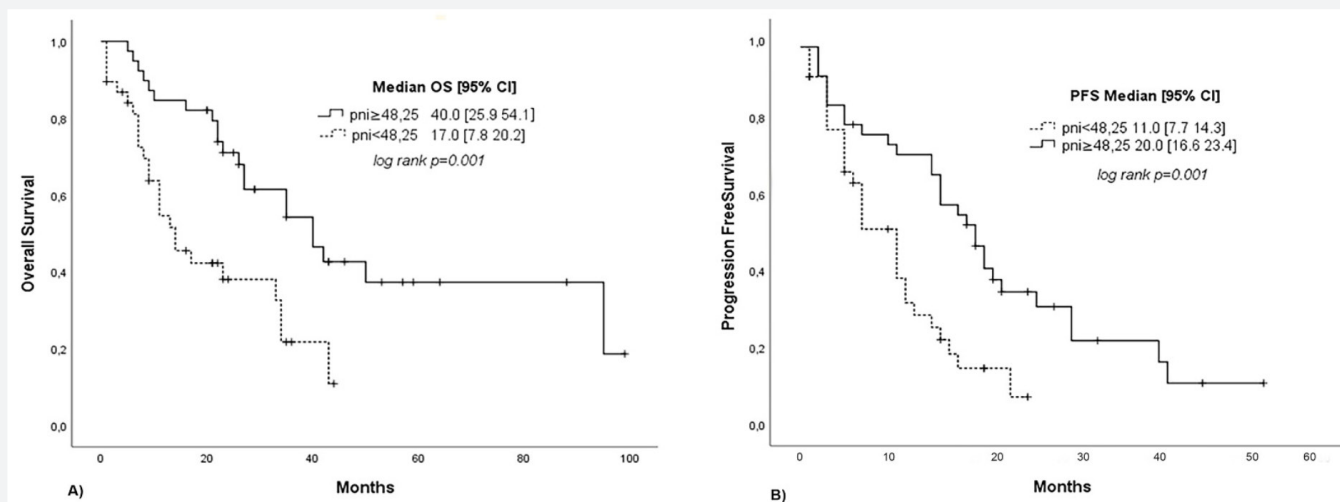


Figure 2. Kaplan-Meier curves showing (A) overall survival and (B) progression-free survival rate stratified by PNI status
PNI: Prognostic Nutritional Index

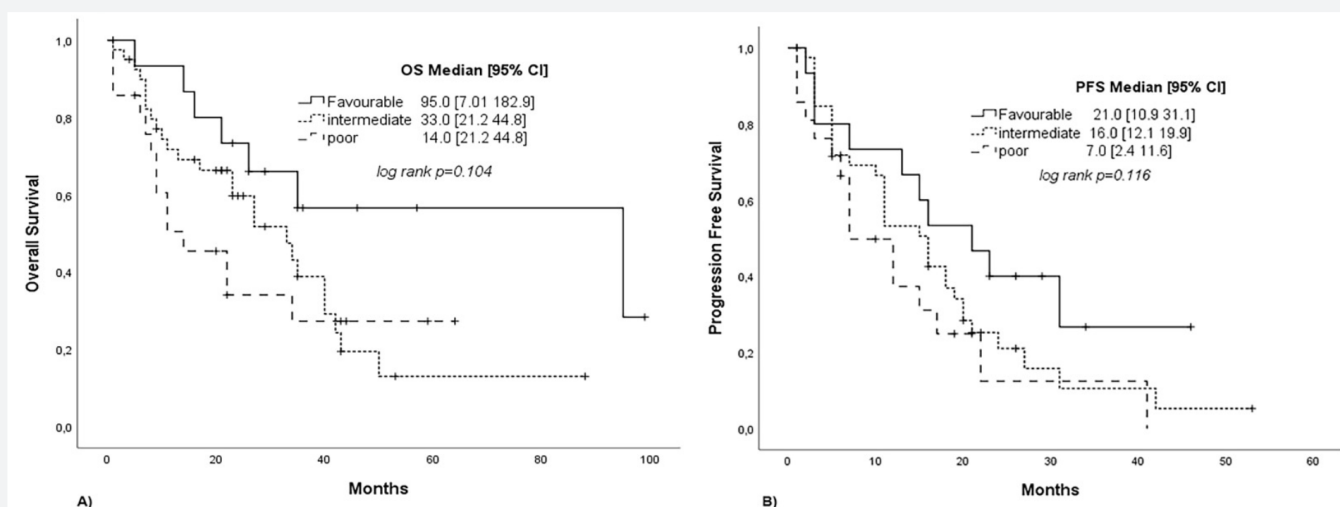


Figure 3. Kaplan-Meier curves showing (A) overall survival and (B) progression-free survival rate stratified by IMDC score
IMDC: International Metastatic RCC Database Consortium

DISCUSSION

In our study, in mRCC patients given sunitinib or pazopanib treatment, significantly shorter OS and PFS were observed in patients with low pretreatment PNI. In addition, while low PNI was a marker for both OS and PFS in multivariate analyses, ECOG-PS was also a marker for OS and IMDC score for PFS.

The nutritional status and immune system are affected by the development and progression of the tumor^{15,16}. When tumor progression occurs, a systemic inflammation develops and the nutritional status worsens¹⁷. Lymphocytes have an important role in cell-mediated immunity, which is one of the important defense mechanisms against cancer in the body¹⁷. Low lymphocyte count is a parameter that indicates suppression of the immune system, and also creates a favorable microenvironment for tumor development and progression¹⁸. PNI is considered as a marker reflecting inflammatory and nutritional status since it is a parameter calculated by lymphocyte count and albumin levels¹⁷.

PNI was initially used as a marker to predict postoperative complications in patients undergoing gastrointestinal system surgery⁷. In a study involving operated gastric cancer patients, significantly longer OS and disease-free survival durations were observed in those with high PNI¹⁹. In a study on colon cancers, it was seen that patients with high PNI had fewer postoperative complications and longer survival⁸.

The prognostic effect of PNI in other cancer types has also been evaluated. In the study involving operated lung cancers, patients with low PNI had more postoperative complications and the survival time was found to be significantly shorter in

these patients¹⁰. In patients with castration-resistant prostate cancer, who received abiraterone acetate, the pre-treatment PNI was low, which is seen as a negative prognostic factor for overall survival²⁰.

Studies evaluating the prognostic effect of PNI in RCC are limited. In the study by Jeon et al.¹¹, PNI was found to be an independent predictive factor for OS in RCC patients who underwent nephrectomy. In the study of Kang et al.¹², in RCC patients who underwent nephrectomy, dynamic changes in preoperative and postoperative PNI were found to be an independent predictive factor for OS. Kim et al.²¹ showed PNI as an independent risk factor for recurrence-free survival and cancer-specific survival in nonmetastatic RCC patients who underwent nephrectomy. In another study, PNI in RCC patients who underwent nephrectomy is a better predictive factor for survival compared to inflammatory indices such as Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio²².

TKI is an important treatment option currently used for mRCC. There are limited studies evaluating the effect of PNI on survival in mRCC patients receiving TKI. In a multicenter retrospective study conducted by Yasar et al.²³, the relationship between the survival and median PNI was evaluated in mRCC patients receiving targeted therapy, and a shorter survival time was observed with low PNI. Similarly, in the study of Kwon et al.¹³, mRCC patients who received targeted therapy showed a shorter survival time than those with low PNI. In another single-center retrospective study, shorter OS and PFS were observed in those with low PNI in mRCC who received first-line TKI¹⁴. In our study, similar to these studies, significantly shorter OS and PFS were observed in those with low PNI.

Table 1. Patient characteristics stratified by the presence of low PNI (<48.25)

	PNI <48.25 (n=38)	PNI ≥48.25 (n=39)	Total n (%)	p
Sex				
Female	9 (23.7)	11 (28.2)	20 (26)	0.651
Male	29 (76.3)	28 (71.8)	57 (74)	
Histology				
Non-clear cell	8 (21.1)	8 (20.5)	16 (20.8)	0.953
Clear cell	30 (78.9)	31 (79.5)	61 (79.2)	
Age (years)				
<65	19 (50)	26 (66.7)	45 (58.4)	0.138
≥65	19 (50)	13 (33.3)	32 (41.6)	
ECOG-PS				
0-1	34 (89.5)	37 (94.9)	71 (92.2)	0.377
≥2	4 (10.5)	2 (5.1)	6 (7.8)	
IMDC				
Poor	15 (39.5)	6 (15.4)	21 (27.3)	0.019
Intermediate	19 (50)	21 (53.8)	40 (51.9)	
Favourable	4 (10.5)	12 (30.8)	16 (20.8)	
CNS metastasis				
Yes	1 (2.6)	7 (17.9)	8 (10.4)	0.028
No	37 (97.4)	32 (82.1)	69 (89.6)	
Lung metastasis				
Yes	29 (76.3)	29 (74.4)	58 (75.3)	0.842
No	9 (23.7)	10 (25.6)	19 (24.7)	
Liver metastasis				
Yes	13 (34.2)	7 (17.9)	20 (26)	0.104
No	25 (65.8)	32 (82.1)	57 (74)	
Treatment type		0 (0)	0 (0)	
Pazopanib	15 (39.4)	15 (38.5)	30 (39)	0.827
Sunitinib	23 (60.5)	24 (61.5)	47 (61)	
RECIST				
CR	1 (2.6)	0 (0)	1 (1.3)	0.153
PR	16 (42.1)	26 (66.7)	42 (54.5)	
SD	7 (18.4)	4 (10.3)	11 (14.3)	
PD	14 (36.8)	9 (23.1)	23 (29.9)	
Survival				
Ex	25 (65.8)	21 (53.8)	46 (59.7)	0.285
Alive	13 (34.2)	18 (46.2)	31 (40.3)	

PNI: Prognostic Nutritional Index, ECOG-PS: Eastern Cooperative Oncology Group-Performance score, IMDC: International metastatic RCC data base consortium, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, CNS: Central nervous system

The IMDC risk score has an important prognostic feature for survival in mRCC. In our study, there was a numerical difference among IMDC favorable, intermediate, and poor risk groups in both OS and PFS, but due to the small number of our patients, no significant differences were detected in the Kaplan-Meier graphic (Figure 3). However, in the multivariate analysis, we showed the IMDC risk score as a marker for PFS (Table 3).

Study Limitations

There are some limitations of our study. First of all, it is a single-center retrospective study and secondly, the number of patients is small.

CONCLUSION

In patients with mRCC treated with sunitinib or pazopanib as first-line targeted therapy, we have shown that low pretreatment PNI is related to poor PFS and OS and it improves the accuracy of a known prognostic model. Future prospective trials should try to validate the comprehensive nutritional-immune components that are now being added to the newly developed predictive model for mRCC patients.

Ethics

Ethics Committee Approval: Approval was obtained from the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical

Table 2. Univariate and multivariate analyses for prognostic factors on progression-free survival

Variable	Univariable		Multivariable	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age (≥65 years)	1.14 (0.68 1.93)	0.616		
Man vs women	1.18 (0.63 1.99)	0.707		
Histology (non-clear vs. clear)	0.77 (0.39 1.54)	0.461		
ECOG (0-1 vs. 2)	0.50 (0.20 1.25)	0.138		
PNI (<48.25 vs. ≥48.25)	2.37 (1.35 4.16)	0.003	2.12 (1.17 3.83)	0.013
IMDC		0.041		0.050
Favourable	1		1	
Intermediate	1.65 (0.81 3.38)	0.171	1.32 (0.71 3.88)	0.244
Poor	2.25 (1.01 5.04)	0.048	2.12 (1.17 3.83)	0.013
Treatment type		0.117		
Pazopanib	1			
Sunitinib	1.67 (0.84 2.98)	0.080		
CNS metastasis	0.47 (0.18 1.21)	0.115		
Lung metastasis	1.57 (0.84 2.93)	0.155		
Liver metastasis	1.52 (0.85 2.73)	0.160		

PNI: Prognostic Nutritional Index, ECOG: Eastern Cooperative Oncology Group, IMDC: International metastatic RCC data base consortium, CNS: Central nervous system, CI: Confidence interval

Table 3. Univariate and multivariate analyses for prognostic factors on overall survival

Variable	Univariable		Multivariable	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age (≥65 years)	1.18 (0.66 2.12)	0.574		
Man vs women	1.02 (0.53 1.94)	0.956		
Histology (non-clear vs. clear)	1.38 (0.70 2.74)	0.349		
ECOG (0-1 vs. 2)	0.18 (0.07 0.45)	0.001	0.22 (0.08 0.60)	0.002
PNI (<48.25 vs. ≥48.25)	2.68 (1.45 4.97)	0.002	2.42 (1.27 4.58)	0.007
IMDC		0.041		0.488
Favourable	1		1	
Intermediate	2.12 (0.87 5.18)	0.099	1.70 (0.68 4.23)	0.257
Poor	2.71 (1.04 7.07)	0.042	1.34 (0.45 3.94)	0.600
Treatment type		0.117		
Pazopanib	1			
Sunitinib	1.68 (0.94 2.98)	0.080		
CNS metastasis	0.47 (0.18 1.21)	0.115		
Lung metastasis	1.57 (0.84 2.93)	0.155		
Liver metastasis	1.52 (0.85 2.73)	0.160		

PNI: Prognostic Nutritional Index, ECOG: Eastern Cooperative Oncology Group, IMDC: International metastatic RCC data base consortium, CNS: Central nervous system, CI: Confidence interval

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Authorship Contributions

Surgical and Medical Practices: S.Y.T, Concept: S.Y.T., M.Y., Design: S.Y.T, M.Y., D.T., Data Collection or Processing: S.Y.T,

Analysis or Interpretation: S.Y.T, M.Y., D.T., Literature Search: S.Y.T, İ.G., Writing: S.Y.T, M.Y.

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The Relationship Between Serum Magnesium Level, Plasma Atherogenic Index and Glomerular Filtration Rate

Serum Magnezyum Düzeyi, Plazma Aterojenik İndeksi ve Glomerüler Filtrasyon Hızı Arasındaki İlişki

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ABSTRACT

Aim: Magnesium is associated with many chronic diseases, especially cardiovascular diseases. The purpose of this study is to evaluate the relationship between serum magnesium level, glomerular filtration rate (GFR) and atherogenic index of plasma (AIP).

Materials and Methods: The data of 214 patients included in the study were analyzed retrospectively. Those with an estimated GFR of 60 mL/minute/1.73 m² and above were grouped as the "high GFR group", and those with an estimated GFR of less than 60 mL/minute/1.73 m² were grouped as the "low GFR group". AIP was calculated by taking the logarithm of the ratio of serum triglyceride level to serum high-density lipoprotein level.

Results: There were 72 patients in the high GFR group and 142 patients in the low GFR group. There was no difference between the groups in terms of serum magnesium level and AIP. The factors related to serum magnesium level and AIP were investigated in the whole study population. A negative correlation was found between serum magnesium level and AIP [Odds ratio (OR): -0.212]. When the factors associated with AIP were examined, AIP was found to be negatively correlated with serum magnesium level (OR: -0.189) whereas positively correlated with body mass index, systolic blood pressure and serum uric acid level (OR: 0.154; 0.276; 0.165, respectively). There was no relationship between AIP and magnesium levels and GFR.

Conclusion: The inverse relationship between serum magnesium level and AIP is consistent with the literature on the relationship between hypomagnesemia and atherogenicity. The lack of a relationship between AIP and serum magnesium level and GFR may be attributed to the small number of patients.

Keywords: Glomerular filtration rate, magnesium, atherogenic index of plasma

ÖZ

Amaç: Magnezyum, kardiyovasküler hastalıklar başta olmak üzere birçok kronik hastalıkla ilişkilendirilmektedir. Bu çalışmanın amacı, serum magnezyum düzeyi, plazma aterojenik indeksi (PAİ) ve glomerüler filtrasyon hızı (GFH) arasındaki ilişkinin değerlendirilmesidir.

Gereç ve Yöntem: Çalışmaya dahil edilen 214 hastanın verileri retrospektif olarak incelendi. Tahmini GFH 60 mL/dakika/1,73 m² ve üzerinde olanlar "yüksek GFH grubu", 60 mL/dakika/1,73 m²'den düşük olanlar "düşük GFH grubu" olarak gruplandırıldı. Serum trigliserit düzeyinin serum yüksek yoğunluklu lipoprotein düzeyine oranının logaritması alınarak PAİ hesaplandı.

Bulgular: yüksek GFH grubunda 72, düşük GFH grubunda 142 hasta yer aldı. Serum magnezyum düzeyi ve PAİ açısından gruplar arasında farklılık saptanmadı. Tüm popülasyonda serum magnezyum düzeyi ile ilişkili faktörler incelendiğinde, sadece PAİ ile magnezyum arasında negatif yönde bir ilişki saptandı [Odds ratio (OR): -0,212]. Yine tüm popülasyonda PAİ ile ilişkili faktörler incelendiğinde, PAİ ile serum magnezyum düzeyi arasında negatif (OR: -0,189); vücut kitle indeksi, sistolik kan basıncı ve serum ürik asit düzeyi arasında pozitif yönde bir ilişki saptandı (sırasıyla; OR: 0,154; 0,276; 0,165). Gerek PAİ, gerekse magnezyum düzeyleri ile tahmini glomerüler filtrasyon hızı arasında ilişki saptanmadı.

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Sonuç: Serum magnezyum düzeyi ile PAİ arasındaki ters yönlü ilişki, hipomagnezeminin aterojenite ile ilişkisine dair genel literatür bilgisi ile uyumludur. PAİ ve serum magnezyum düzeyi ile GFH arasında bir ilişkinin saptanmamış olması, hasta sayısının azlığına bağlanabilir.

Anahtar Kelimeler: Glomerüler filtrasyon hızı, magnezyum, plazma aterojenik indeksi

INTRODUCTION

Magnesium is the major intracellular cation in the body after potassium and is a cofactor of more than 300 enzymes that play role in many vital processes, including blood pressure regulation, glucose metabolism and lipid peroxidation¹. The total body magnesium amount in an adult is approximately 22-26 g, and 50-60% of this amount is found in the bones. Serum levels of magnesium reflect approximately 1% of the intracellular component (1.2-2.5 mg/dL). From the perspective of the chronic kidney disease (CKD) course, magnesium retention is expected to increase, especially at values below 30 mL/minute/1.73 m², together with the decrease in glomerular filtration rate (GFR)². Western-style diet with low vegetable-fruit content, malabsorption, use of diuretics and laxatives are the main causes of hypomagnesemia³. It has been suggested that hypomagnesemia causes an increase in inflammation, oxidative stress and lipid peroxidation and thus plays a role in the pathogenesis of diabetes, metabolic syndrome, cardiovascular diseases and endothelial damage⁴⁻¹⁰. Information on magnesium metabolism in the CKD process is limited. In recent years, the number of studies showing that hypomagnesemia may play a role in the pathogenesis, progression and complications of CKD has been increasing¹¹⁻¹⁶.

Dyslipidemia is a major risk factor for cardiovascular diseases and related complications, affecting approximately half of the population in developed countries. Despite being so common, awareness and effective treatment rates are quite low¹⁷. CKD is a process in which the frequency of hyperlipidemia increases with decreasing GFR. On the other hand, hyperlipidemia has also been reported to accelerate CKD progression^{18,19}. Hypomagnesemia is one of the lesser known and partially newly defined risk factors that may be associated with hyperlipidemia^{20,21}.

In order to determine the cardiovascular risk profile associated with hyperlipidemia, inexpensive and easy-to-use indices including serum lipid profile and some hematological/biochemical parameters have been defined in clinical practice. Atherogenic index of plasma (AIP), being one of them, is the logarithm of the ratio obtained by dividing the plasma triglyceride level by the plasma high-density lipoprotein (HDL) level, and it has been reported to be well correlated with cardiovascular risk²²⁻²⁴.

The aim of this study is to compare the high GFR and low GFR groups in terms of serum magnesium level and AIP, and to

evaluate the relationship between serum magnesium level, GFR and AIP.

MATERIALS AND METHODS

Electronic medical records of 1412 adult patients attending nephrology outpatient clinic at the Tekirdağ Namık Kemal University Hospital between June 2021 and January 2022 were reviewed retrospectively. The following exclusion criteria were used: taking magnesium replacement and lipid-lowering agent, being on dialysis treatment; having acute/chronic diarrhea, reduced oral intake, diabetes mellitus, hereditary renal tubular disorders, acute kidney injury (in last 6 weeks) and active systemic infectious, inflammatory or malignant disease. Two hundred and fourteen patients were included in the evaluation. Estimated glomerular filtration rate (tGFR) value was calculated with the CKD-EPI formula²⁵. Those with a tGFR value of 60 mL/minute/1.73 m² and above were grouped as the "high-GFR group", and those below 60 mL/minute/1.73 m² were grouped as the "low-GFR group". AIP value is calculated by taking the logarithm of the ratio of serum triglyceride level to serum HDL level and body mass index (BMI) was calculated by dividing the patient's body weight (kg) by the square of the patient's height (m²).

Statistical Analysis

Statistical analysis was performed using Statistical Package of Social Science (SPSS) version 25 software. Compatibility with normal distribution of parametric variables was evaluated using Shapiro-Wilk test. The Student's t-test was applied in the comparison of normally distributed data, and the Mann-Whitney U test for non-normally distributed data. The chi-square test was used to compare categorical variables. Multivariate linear regression analysis was performed for the parameters found to be associated with serum magnesium level and AIP as a result of Pearson's correlation analysis.

P value < 0.05 were regarded as statistically significant.

RESULTS

General Characteristics of the Study Group

Of the 214 patients included in the study, 48.6% were male and 51.4% were female. The mean age of the patients was 59.7±14.1 years, and BMI was 29.4±5.4 kg/m². The rate of patients with a diagnosis of hypertension was 83.6%, and the rate of patients with coronary artery disease was 33.6%. The rates of patients using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB); calcium channel blockers (CCB); thiazide and beta blockers

were 64.5%; 34.6%; 40.2% and 41.4%, respectively. The mean serum creatinine level in the study group was 1.66 ± 0.88 mg/dL; mean tGFR was 51.2 ± 28.0 mL/minute/1.73 m², mean serum magnesium level was 1.97 ± 0.26 and the mean AIP was found to be 0.14 ± 0.28 . Serum magnesium levels were similar in patients using and not using thiazide (2.00 ± 0.28 mg/dL vs. 1.95 ± 0.24 mg/dL; $p=0.146$).

Comparison of the Groups

There were 72 patients in the high-GFR group and 142 patients in the low-GFR group. There was no difference between the groups in terms of serum magnesium level and AIP. Serum glucose, uric acid, C-reactive protein levels and proteinuria were higher in the low-GFR group; serum albumin and HDL levels were found to be lower (Table 1). The rates of hypertension and coronary artery disease were found to be higher in the low-GFR group (90.1% vs. 70.8%, $p<0.001$, 43.7% vs 13.9%, respectively, $p<0.001$). There was no difference between the groups in terms of use of ACEI/ARB, CCB, thiazide and beta blockers ($p=0.666$; 0.136; 0.052; 0.783, respectively).

Relationship between serum magnesium level and other parameters

When the entire study group was evaluated by correlation analysis, no correlation was found between tGFR and serum magnesium level. There was a negative correlation between serum magnesium level and serum glucose level, BMI and AIP and a positive correlation was found between serum creatinine, parathormone (PTH) and phosphorus levels. As a result of the multiple linear regression analysis performed by including serum creatinine, glucose and PTH values, AIP and BMI, it was observed that only the relationship between AIP and magnesium continued in the negative direction (OR: -0.212, $p=0.006$) (Table 2). Phosphorus was not included in the multiple regression analysis because the serum phosphorus level is directly affected by the serum PTH level.

Parameters affecting AIP

When the entire study group was evaluated, no correlation was found between AIP and tGFR. There was a positive correlation

Table 1. Clinical characteristics and laboratory findings of the study group

	High GFR group (n=72)	Low GFR group (n=142)	p
Age (year)	55 (22-80)	64 (19-93)	<0.001
Male n (%)	31 (43.1)	73 (51.4)	0.248
BMI (kg/m ²)	28.9 (16.9-47.9)	29.2 (19.3-45.8)	0.276
Hypertension n (%)	51 (70.8)	128 (90.1)	<0.001
CAD n (%)	10 (13.9)	62 (43.7)	<0.001
SBP (mmHg)	130 (100-230)	140 (100-220)	0.024
DBP (mmHg)	80 (60-140)	80 (55-120)	0.414
Glucose (mg/dL)	100 (76-176)	108 (76-179)	0.020
Creatinine (mg/dL)	0.85 (0.48-1.39)	1.88 (0.60-5.34)	<0.001
eGFR (mL/minute/1.73 m ²)	84 (60-125)	33 (10-59)	<0.001
Uric acid (mg/dL)	5.4 (2.3-7.7)	6.4 (3.6-14)	<0.001
Sodium (mEq/L)	139 (127-144)	139 (126-146)	0.314
Potassium (mEq/L)	4.4 $\pm$ 0.4	4.7 $\pm$ 0.6	<0.001
Calcium (mg/dL)	9.4 $\pm$ 0.5	9.2 $\pm$ 0.5	0.089
Phosphorus (mg/dL)	3.5 $\pm$ 0.7	3.8 $\pm$ 0.7	0.003
Magnesium (mg/dL)	1.95 $\pm$ 0.22	1.99 $\pm$ 0.27	0.220
Albumin (g/dL)	4.5 (2.2-5.2)	4.3 (2.5-5.2)	0.010
CRP (mg/dL)	2.8 (0.2-32)	4.5 (0.2-51)	0.006
Total cholesterol (mg/dL)	200 (122-458)	192 (98-334)	0.101
LDL (mg/dL)	117 (53-362)	110 (27-216)	0.065
HDL (mg/dL)	50 (23-100)	45 (24-83)	0.010
TG (mg/dL)	150 (43-333)	150 (44-630)	0.551
AIP (logTG/HDL)	0.10 $\pm$ 0.28	0.16 $\pm$ 0.29	0.116
Spot urine PCR (mg/gr)	0.17 (0.01-9.93)	0.44 (0.01-7.8)	<0.001

*Data are expressed as "mean $\pm$ SD" or median (min-max).

AIP: Plasma atherogenic index, BMI: Body mass index, CAD: Coronary artery disease, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, PCR: Protein-to-creatinine ratio, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride

between AIP and serum uric acid level, BMI, systolic blood pressure (SBP) and diastolic blood pressure and a negative correlation was found with the serum magnesium level. As a result of multiple linear regression analysis in which these parameters were included, there was a positive correlation between AIP and BMI and between SBP and serum uric acid level (OR: 0.154; 0.276; 0.165, $p=0.032$; 0.004; 0.016, respectively). A negative correlation (OR: -0.189, $p=0.006$) was observed between AIP and serum magnesium level (Table 3).

DISCUSSION

In our study, high-GFR and low-GFR groups were similar in terms of serum magnesium level and AIP. No correlation was found between tGFR and serum magnesium level, and between tGFR and AIP in the entire study group. In addition, there was a negative correlation between AIP and serum magnesium level; a positive correlation was found between BMI, SBP and serum uric acid levels, and this result of our study seems to be compatible with the prevailing literature since it fits the known major cardiovascular risk profile.

Although hypomagnesemia is held responsible for increased morbidity and mortality in cardiovascular diseases and diabetes as well as in CKD, the cause-effect relationship in this area is still unclear^{26,27}. The most valid and current hypothesis put forward in this process is that hypomagnesemia increases vascular calcification. In addition, it has been reported that inflammation exacerbated in the presence of hypomagnesemia has been reported to accelerate the atherosclerotic process^{28,29}.

Table 2. Parameters related to serum magnesium level

	Correlation		Multiple linear regression	
	r	p	OR	p
BMI	-0.171	0.017	-0.083	0.286
Creatinine	0.156	0.022	0.040	0.666
Glucose	-0.192	0.005	-0.114	0.129
PTH	0.291	<0.001	0.143	0.118
AIP	-0.217	0.001	-0.212	0.006

BMI: Body mass index, PTH: Parathyroid hormone, AIP: Atherogenic index of plasma, OR: Odds ratio (with 95% confidence interval)

Table 3. Parameters related to plasma atherogenic index

	Correlation		Multiple linear regression	
	R	p	OR	p
BMI	0.247	0.001	0.154	0.032
SBP	0.288	<0.001	0.276	0.004
DBP	0.199	0.003	-0.080	0.408
Uric acid	0.167	0.016	0.165	0.016
Magnesium	-0.217	0.001	-0.189	0.006

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, OR: Odds ratio (with 95% confidence interval)

Accordingly, it has been reported that interventions to increase serum magnesium level reduce serum phosphorus level, reduce joint pain and inflammation by reducing soft tissue calcification, decrease carotid intima-media thickness, and reduce mortality.

However, the majority of these studies were conducted in the hemodialysis population^{14,29-31}. The number of studies on this subject in patients with CKD in earlier stages is few. In one of these studies, a negative correlation was reported between serum magnesium level and endothelial dysfunction³². Another study in stage 3 and 4 CKD patients reported that serum magnesium level increased with decreasing GFR, and this rise increased the frequency of cardiovascular events and mortality²⁶. In our study, although it was not statistically significant, a negative correlation was found between serum magnesium level and GFR ($r=-0.125$). On the other hand, although there was a significant positive correlation between serum magnesium and creatinine levels, it became non-significant in multiple regression analysis.

It is well known that, as eGFR declines, the frequency of cardiovascular events increases significantly, which are the main causes of death in the CKD group. Serum lipid levels are among the major components of the cardiovascular risk profile. It is accepted that dyslipidemia also contributes to CKD progression³³. Important components of dyslipidemia in the CKD course include high serum triglyceride levels, low serum HDL levels, and HDL dysfunction even if its level is normal^{34,35}. Although there are many studies evaluating the indicators of hyperlipidemia in CKD patients, the only study in the literature evaluating the relationship between GFR and AIP belongs to Zhou and Shang³⁶. 15836 patients were included in this study, and a strong negative correlation was found between AIP and GFR. In addition, it has been reported that this relationship is stronger in the presence of male gender, high BMI, black race, age less than 50, hypertension and/or diabetes. Therefore, it was concluded that the risk of the decline in GFR could be predicted through AIP. In our study, although not statistically significant, a negative correlation was found between AIP and GFR ($r=-0.076$).

In our study, a significant negative correlation was found between AIP and serum magnesium level, and a positive significant correlation was found between uric acid, SBP and BMI, and our findings are consistent with the literature^{24,36-38}. Although there are many studies reporting that magnesium is associated with atherogenicity among these parameters, information about the mechanism of this relationship, the therapeutic use of magnesium and target serum levels is not sufficient. The general conclusion in the literature is that hypomagnesemia adversely affects the serum lipid profile and related indicators^{20,39}. In a study by Cambray et al.²¹, it was

shown that the lipid profile worsened and carotid intima-media thickness increased in the presence of hypomagnesemia in the CKD population. In a case-control study by Dey et al.⁴⁰, it was reported that hypomagnesemia worsened atherogenic dyslipidemia parameters in the CKD group.

Study Limitations

1. In this single-center study, our number of cases was low compared to similar studies in the literature.
2. Since the relationship of magnesium and lipid parameters with GFR change over time was not evaluated, no comment could be made on the contribution of these parameters to CKD progression.

CONCLUSION

In our study, the finding of a relationship between serum magnesium level and AIP in addition to known cardiovascular risk factors supports the view that hypomagnesemia contributes to atherogenicity. Although the number of studies in this area is increasing, there is not enough data to support the use of magnesium for therapeutic purposes. Particular care should be taken in this regard, due to the predisposition to hypermagnesemia in patients with advanced CKD. In conclusion, we think that the relationship of magnesium with cardiovascular and renal survival in both healthy and CKD populations should be evaluated in large population-based cohorts with biochemical and functional parameters that will be repeated over a long period of time.

Ethics

Ethics Committee Approval: The study protocol was prepared in accordance with the Declaration of Helsinki and approved by the Tekirdağ Namık Kemal University Non-Interventional Research Ethics Committee (protocol no: 2021.280.12.03, date: 28.12.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.B., Design: N.B., Data Collection or Processing: N.B., Ö.E., V.Y.K., A.Ç., Analysis or Interpretation: N.B., G.Ö., Literature Search: N.B., V.Y.K., Writing: N.B.

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Evaluation of Mental Health Literacy Status of Patients Admitted to the Family Medicine Outpatient Clinic

Aile Hekimliği Polikliniğine Başvuran Hastaların Ruh Sağlığı Okuryazarlığı Durumunun Değerlendirilmesi

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ABSTRACT

Aim: Mental health literacy (MHL) refers to knowledge and beliefs regarding recognizing, managing, and preventing mental health disorders. It is critical in the early diagnosis of mental health diseases. This study aimed to determine the symptom levels of individuals for anxiety and depression and to evaluate their MHL status.

Materials and Methods: This prospective study was designed as descriptive and single-centered. The study was performed with patients between the ages of 18 and 65 years, who were admitted to the Family Medicine Outpatient Clinic of a tertiary hospital and who met the inclusion criteria. The participants' sociodemographic and medical characteristics were questioned by the Patient Information Form. Symptom levels for anxiety and depression were evaluated with the Hospital Anxiety and Depression Scale (HADS), and MHL levels were determined with the Mental Health Literacy Scale (MHLS).

Results: The mean age of 327 participants was 38.95 ± 11.94 years, and most were female ($n=216$; 66.1%). According to HADS, the mean anxiety score was 7.90 ± 4.54 , and the mean depression score was 6.97 ± 4.36 . The mean total MHLS score was 14.05 ± 3.49 , the mean knowledge subscale score was 7.56 ± 1.93 , the mean belief subscale score was 4.17 ± 1.83 , and the mean resource subscale score was 2.28 ± 1.54 . An inverse and significant correlation was determined between age and MHLS total score ($p=0.001$). There was a significant difference in education levels regarding MHLS total score ($p=0.000$). An inverse and significant correlation was observed between MHL total score and HADS anxiety and depression scores ($p=0.041$, $p=0.000$, respectively).

Conclusion: In our study, MHL was determined to be at a moderate level, and it was lower in those with high symptom levels for anxiety and depression. On the other hand, MHL level was also negatively affected by advanced age and the presence of chronic diseases, and it was higher in those with higher education levels, those who were married, and those who worked in any job.

Keywords: Family medicine, anxiety, depression, mental health, mental health literacy

ÖZ

Amaç: Ruh sağlığı okuryazarlığı (RSOY) ruh sağlığı bozukluklarını tanıma, yönetme ve önlemeye yönelik bilgi ve inançları ifade etmektedir. Ruh sağlığı bozukluklarının erken teşhisinde kritik öneme sahiptir. Bu çalışmanın amacı; kişilerin anksiyete ve depresyona yönelik semptom düzeylerini belirlemek ve RSOY durumlarını değerlendirmektir.

Gereç ve Yöntem: Bu prospektif çalışma tanımlayıcı ve tek merkezli olarak tasarlandı. Çalışma üçüncü basamak bir hastanenin Aile Hekimliği Polikliniği'ne başvuran 18-65 yaş arası hastalardan çalışmaya dahil edilme kriterlerini karşılayanlar ile yapıldı. Katılımcıların sosyodemografik ve tıbbi özellikleri hasta bilgi formu ile sorgulandı. Hastane Anksiyete ve Depresyon Ölçeği (HADÖ) ile anksiyete ve depresyona yönelik semptom düzeyleri, Ruh Sağlığı Okuryazarlığı Ölçeği (RSOYÖ) ile RSOY düzeyleri değerlendirildi.

Bulgular: Çalışmaya dahil edilen 327 hastanın yaş ortalaması $38,95 \pm 11,94$ yıl olup çoğu kadın ($n=216$; %66,1) idi. HADÖ'ye göre ortalama anksiyete skoru $7,90 \pm 4,54$, depresyon skoru $6,97 \pm 4,36$ idi. Ortalama total RSOYÖ skoru $14,05 \pm 3,49$, bilgi odaklı RSOY skoru $7,56 \pm 1,93$, inanç odaklı RSOY

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skoru $4,17 \pm 1,83$, kaynak odaklı RSOY skoru $2,28 \pm 1,54$ idi. Yaş ile RSOYÖ total skoru arasında ters yönlü ve anlamlı bir ilişki bulundu ($p=0,001$). Eğitim durumları arasında RSOY toplam skoru açısından anlamlı bir farklılık saptandı ($p=0,000$). RSOY total skoru ile HADÖ anksiyete ve depresyon skorları arasında ters yönlü ve anlamlı bir ilişki bulundu (sırasıyla $p=0,041$; $p=0,000$).

Sonuç: Çalışmamızda RSOY orta düzeyde bulunmuş olup anksiyete ve depresyona yönelik semptom düzeyleri yüksek olanlarda daha düşük olarak saptandı. Bununla birlikte RSOY düzeyinin ilerleyen yaş ve kronik hastalık varlığından da olumsuz etkilendiği ve eğitim düzeyi yüksek olanlarda, evli olanlarda, herhangi bir işte çalışanlarda daha yüksek olduğu görüldü.

Anahtar Kelimeler: Aile hekimliği, anksiyete, depresyon, ruh sağlığı, ruh sağlığı okuryazarlığı

INTRODUCTION

According to the World Health Organization (WHO), mental health is defined as a state of well-being in which a person realizes his/her potential, copes with the normal stresses of life, works efficiently, and contributes to himself and society¹.

Deterioration in mental health may occur due to exposure to stress, genetics, nutrition, perinatal infections, and environmental hazards. Many mental health disorders such as depression, bipolar disorder, psychotic disorders such as schizophrenia, dementia, and autism, which can occur with abnormalities in thoughts, perceptions, emotions, and behaviors, are well-known².

Mental health disorders are a major concern worldwide³. WHO reported that mental disorders could occur in approximately 12% of the entire population at any given time in the European Region⁴. In Turkey, the rate of mental illnesses detected in the "Turkish Mental Health Profile Study", the first and only scaled study reporting a nationwide prevalence, is 17.2%. More than 20 years have passed since this research, and it should not be overlooked that there have been significant changes in Turkey's health system, as well as in its social and population structure during this time⁵. In the light of this information, it can be considered that people are likely to encounter a mental health disorder in themselves or their relatives at any time during their lifetime. In this context, the concept of mental health literacy (MHL), an extension of health literacy that continues to develop, is vital in terms of early diagnosis and intervention of mental health disorders. According to Jorm, who first defined this concept, MHL refers to individuals' ability to understand and identify mental disorders, their etiology, how and where to seek help for mental health, and the management and prevention of mental health disorders^{6,7}.

As MHL increases, people's awareness of the symptoms of mental health disorders and their behavior of using treatment resources correctly will increase, and thus, an improvement in mental health is expected. Those with low MHL levels may not realize that when a mental health disorder occurs in them or their relatives, it is a disease that requires medical attention. This situation may result in less healthcare, delays in diagnosis, and worsening prognosis^{8,9}.

MHL is a concept that is being researched more every day since it plays a decisive role in the mental health of individuals and society. However, there is not enough research on MHL in Turkey. This study aimed to determine the symptom levels of individuals for anxiety and depression and to evaluate the MHL status.

MATERIALS AND METHODS

This prospective research was designed as a descriptive and single-centered study. Ethical permission for the study was obtained from the Gaziosmanpaşa Training and Research Hospital Local Ethics Committee (approval no: 371, dated: 24.11.2021). The study was performed as per the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant before the study.

Study Design

Participants were selected from patients referred to the Family Medicine Outpatient Clinic of a tertiary hospital between December 27, 2021 and January 21, 2022. Three hundred and twenty-seven people who had no known mental health problems and a history of psychiatric drug use, who were between the ages of 18 and 65 years, and who agreed to participate were included in the study. Those under the age of 18 years and over the age of 65 years, those with known psychiatric disease and psychiatric drug use, those with a disability to communicate, and those who were illiterate were excluded from the study.

Based on the sample size calculation made with G-power analysis using the simple random sampling method from the study population, the minimum required number of participants was 291 with a 95% confidence interval.

Data Collection Tools

In the study, the Patient Information Form, Hospital Anxiety and Depression Scale (HADS), and Mental Health Literacy Scale (MHLS) were used to obtain data.

Patient Information Form: A patient information form was formulated, which we prepared using the literature, including the participants' sociodemographic characteristics (age, gender, marital status, working status, educational status), and

questioned general health status (presence of chronic diseases, medication, alcohol, and cigarette use).

HADS: HADS was developed by Zigmond and Snaith¹⁰ in 1983 to determine the risk of anxiety and depression to measure the level and change in severity. The Turkish validity and reliability study was performed by Aydemir et al.¹¹ in 1997. This four-point Likert-type scale includes 14 questions in total and it consists of two subscales: HADS-anxiety (HADS-A) and HADS-depression (HADS-D). In the validity and reliability study, the cut-off score was 10 for HADS-A and 7 for HADS-D. Those who score above these values are considered at risk for anxiety and depression. The Cronbach's alpha coefficient was 0.8525 for HADS-A and 0.7784 for HADS-D¹¹.

MHLS: The MHLS was developed by Jung et al.⁹ in 2016. The Turkish validity and reliability study was performed by Göktaş et al.¹² in 2019. The scale consists of three sub-dimensions and 22 items. There are 11 items in the knowledge subscale, 8 items in the belief subscale, and 4 items in the resource subscale. The 18 questions in the first two subscales are in six-point Likert type, and the answers are given as "strongly agree, agree, undecided, disagree, strongly disagree, do not know". The answers to 4 questions in the resource subscale are "yes" and "no". When the answers to the questions are "strongly agree", "agree", and "yes", "1 point" is given, other answers are considered as "0 points". The score that can be obtained from the scale varies between 0 and 22, and as the score increases, the MHL level increases. The Cronbach's alpha coefficient was calculated as 0.71 in the Turkish version of the scale^{9,12}.

Statistical Analysis

While evaluating the data obtained in the study, IBM Statistical Package for the Social Sciences statistics 22 software was used for statistical analysis. The suitability of the parameters to the normal distribution was evaluated by the Kolmogorov-Smirnov and Shapiro-Wilks tests, and the parameters did not show normal distribution. While evaluating the data, in addition to descriptive statistical methods (mean, standard deviation, frequency), the Kruskal-Wallis test was employed to compare the parameters between more than two groups in the comparison of quantitative data, and the Dunn's test revealed the group that caused the difference. The Mann-Whitney U test was used for the comparison of parameters between two groups. The Spearman's rho correlation analysis was used to analyze the correlations between parameters. The statistical significance was determined at the $p < 0.05$ level.

RESULTS

The ages of 327 participants ranged from 18 to 65 years, with a mean of 38.95 ± 11.94 years. 66.1% ($n=216$) of the participants were female, 62.4% ($n=204$) were married, and 39.4%

($n=129$) were university graduates. While 54.1% ($n=177$) were unemployed, the majority of the employees (38.7%; $n=58$) were working in the private sector. 30.3% ($n=99$) were active smokers, 37.6% ($n=123$) had any chronic disease. The distribution of descriptive information about the participants is presented in Table 1.

As demonstrated in Table 2, the mean MHLS total score of the participants was 14.05 ± 3.49 (4-22). The mean knowledge subscale score was 7.56 ± 1.93 (2-10), the mean belief subscale score was 4.17 ± 1.83 (0-8), and the mean resource subscale score was 2.28 ± 1.54 (0-4). The mean HADS-A score was

Table 1. Distribution of descriptive characteristics of the participants

		n	%
Gender	Female	216	66.1
	Male	111	33.9
Marital status	Married	204	62.4
	Single	123	37.6
Working status	Unemployed	177	54.1
	Employed	150	45.9
Occupational classification (n=150)	Worker	21	14.0
	Officer	43	28.7
	Self-employment	28	18.7
	Private sector	58	38.7
Educational status	Literate	18	5.5
	Primary school	80	24.5
	Middle school	33	10.1
	High school	67	20.5
Smoking status	University	129	39.4
	Active smoker	99	30.3
	Ex-smoker	61	18.7
Alcohol use	Never smoked	167	51.1
	No	260	79.5
Presence of chronic disease	Yes	67	20.5
	No	204	62.4
Chronic disease type (n=123)	Yes	123	37.6
	Cardiovascular diseases	20	16.3
	Endocrinological diseases	29	23.6
	Pulmonary disease	11	8.9
	Other	43	35
Drug use	Cardiological+Endocrinological	10	8.1
	Multiple diseases	10	8.1
	No	235	71.9
	Yes	92	28.1

7.90±4.54 (0-21), the mean HADS-D score was 6.97±4.36 (0-21), and it was observed that the values were below the cut-off values determined for the Turkish form (Table 2).

When HADS and MHLS scores were compared, a significant inverse correlation was determined between the HADS-A score and MHLS total score and resource subscale score of MHLS ($p=0.041$, $p=0.001$, respectively). There was a significant inverse correlation between the HADS-D score and MHLS total score, knowledge subscale score of MHLS, and resource subscale score of MHLS ($p=0.000$, $p=0.004$, $p=0.000$, respectively). Findings related to the comparison of HADS and MHLS results are summarized in Table 3.

Table 2. Distribution of total scores from scales and sub-dimension scores

	Minimum-maximum	Mean±SD	Median
HADS			
HADS-A	0-21	7.90±4.54	7
HADS-D	0-21	6.97±4.36	6
MHLS total score	4-22	14.05±3.49	14
MHLS subscales			
Knowledge subscale MHLS	2-10	7.56±1.93	8
Belief subscale MHLS	0-8	4.17±1.83	4
Resource subscale MHLS	0-4	2.28±1.54	2

Data presented as mean±SD and minimum-maximum.

HADS: Hospital Anxiety Depression Scale, HADS-A: Hospital Anxiety Depression Scale-Anxiety, HADS-D: Hospital Anxiety Depression Scale-Depression, MHLS: Mental Health Literacy Scale, SD: Standard deviation

Table 3. Correlation of the scores obtained from the HAS scale and the total score and sub-dimension scores of the MHLS

		HADS	
		HADS-A	HADS-D
MHLS total score	r	-0.113	-0.220
	p	0.041*	0.000*
MHLS subscales			
Knowledge subscale MHLS	r	-0.039	-0.158
	p	0.480	0.004*
Belief subscale MHLS	r	-0.051	-0.053
	p	0.355	0.336
Resource subscale MHLS	r	-0.181	-0.241
	p	0.001*	0.000*

Spearman's rho correlation test, * $p<0.05$.

HADS: Hospital Anxiety Depression Scale, HADS-A: Hospital Anxiety Depression Scale-Anxiety, HADS-D: Hospital Anxiety Depression Scale-Depression, MHLS: Mental Health Literacy Scale

A significant inverse correlation was determined between age and MHLS total score, knowledge, and resource subscale scores of MHLS ($p=0.001$, $p=0.003$, $p=0.000$, respectively).

Data for the evaluation of the MHLS results according to the descriptive characteristics of the patients are presented in Table 4. There was no statistically significant difference between the genders regarding total MHLS score, knowledge, and belief subscale MHLS scores ($p>0.05$). However, men's resource subscale scores of MHLS were significantly higher than women's ($p=0.031$). The knowledge and resource subscale MHLS scores of the married were significantly higher than the singles ($p=0.007$, $p=0.013$, respectively). When the participants were evaluated according to their employment status, the employees' total MHLS, knowledge, and resource subscale MHLS scores were significantly higher than those of unemployed people ($p=0.003$, $p=0.003$, $p=0.000$; respectively) (Table 4). There were significant differences in education levels in terms of MHL total score, knowledge, and resource subscale MHLS scores ($p=0.000$, $p=0.015$, $p=0.000$; respectively). The results of the post hoc analyses performed to determine from which education level the significance originates are also presented in Table 4.

DISCUSSION

MHL is a multifaceted concept and refers to the knowledge and beliefs that assist in recognizing, managing and preventing mental health disorders⁶. Evaluating people's MHL levels is critical in promoting early diagnosis and not delaying treatment in mental health disorders¹³. This study aimed to investigate the severity of depression and anxiety symptoms in patients admitted to the Family Medicine Outpatient Clinic, to evaluate the MHL levels, and to examine the affecting factors. In the light of the findings obtained, MHL was found to be at a moderate level, and it was lower in those with high symptom levels for anxiety and depression. On the other hand, it was determined that the MHL level was negatively affected by advanced age and the presence of chronic diseases, and it was higher in those with higher education levels, those who were married, and those who worked in any job.

Although MHL is an increasingly researched concept, studies on this subject are generally less in non-western countries. These few studies have revealed low MHL levels in non-western countries¹⁴.

There are few studies on MHL in Turkey^{12,15,16}. One of them is the adaptation study of MHLS to Turkish, including university students. In this study, the average of the total scores obtained from the MHLS was found to be 12, and it was higher (average MHLS total score: 17) in medical faculty students than in other students¹². In another study by Pehlivan et al.¹⁵ performed with university students, more than half of the participants

		MHLS total score	Knowledge subscale MHLS	Belief subscale MHLS	Resource subscale MHLS
		Mean±SD (median)	Mean±SD (median)	Mean±SD (median)	Mean±SD (median)
Gender	Female	14.14±3.47 (14)	7.67±1.87 (8)	4.26±1.81 (4)	2.15±1.56 (2)
	Male	13.86±3.53 (14)	7.35±2.03 (8)	3.98±1.85 (4)	2.53±1.48 (3)
	¹ p	0.494	0.229	0.336	0.031*
Marital status	Married	13.78±3.67 (14)	7.34±1.99 (7)	4.29±1.81 (4)	2.12±1.55 (2)
	Single	14.49±3.14 (15)	7.93±1.77 (8)	3.96±1.85 (4)	2.54±1.49 (3)
	¹ p	0.099	0.007*	0.169	0.013*
Working status	Unemployed	13.49±3.37 (14)	7.29±1.9 (7)	4.14±1.77 (4)	1.99±1.51 (2)
	Employed	14.71±3.53 (15)	7.88±1.92 (8)	4.21±1.91 (4)	2.62±1.5 (3)
	¹ p	0.003*	0.003*	0.536	0.000*
Profession type	Worker	12.81±3.78 (13)	7.57±2.13 (7)	3.62±2.2 (4)	1.71±1.55 (1)
	Officer	16.12±3.35 (17)	8.12±1.83 (9)	4.7±1.75 (5)	3.3±1.15 (4)
	Self-employment	12.89±3.22 (13)	7±1.94 (7)	3.57±1.91 (4)	2.18±1.54 (2)
	Private sector	15.22±3.11(15.5)	8.24±1.8 (8)	4.36±1.81 (5)	2.66±1.48 (3)
	² p	0.000*	0.025*	0.075	0.000*
Educational status	Literate	11.17±4.12 (11)	6.89±2.11(6.5)	3.44±1.82 (4)	0.83±1.42 (0)
	Primary school	12.64±3.14 (12.5)	7.21±1.97 (7)	4±1.83 (4)	1.44±1.39 (1)
	Middle school	13.45±3.02 (13)	7.42±1.8 (8)	3.91±1.86 (4)	1.94±1.3 (2)
	High school	14.3±3.04 (14)	7.45±1.83 (7)	4.18±1.93 (4)	2.6±1.44 (3)
	University	15.34±3.38 (16)	7.96±1.91 (8)	4.43±1.75 (5)	2.93±1.35 (4)
	² p	0.000*	0.015*	0.171	0.000*
Smoking status	Active smoker	13.87±3.3 (14)	7.18±1.92 (7)	4.03±1.78 (4)	2.64±1.35 (3)
	Ex-smoker	14.75±3.82 (15)	7.87±1.85 (8)	4.57±2.01 (5)	2.31±1.57 (3)
	Never smoked	13.89±3.46 (14)	7.67±1.94 (8)	4.1±1.78 (4)	2.06±1.6 (2)
	² p	0.140	0.043*	0.136	0.025*
Alcohol use	No	13.93±3.49 (14)	7.58±1.95 (8)	4.12±1.81 (4)	2.2±1.57 (2)
	Yes	14.49±3.48 (14)	7.49±1.86 (8)	4.37±1.9 (5)	2.58±1.38 (3)
	¹ p	0.286	0.694	0.227	0.097
Presence of chronic disease	No	14.38±3.53 (14)	7.65±1.91 (8)	4.2±1.91 (4)	2.48±1.49 (3)
	Yes	13.5±3.37 (14)	7.41±1.95 (7)	4.12±1.7 (4)	1.95±1.57 (2)
	¹ p	0.028*	0.221	0.501	0.002*
Drug use	No	14.27±3.53 (14)	7.64±1.93 (8)	4.14±1.9 (4)	2.45±1.49 (3)
	Yes	13.47±3.33 (14)	7.36±1.91(7.5)	4.25±1.66 (4)	1.86±1.59 (2)
	¹ p	0.049*	0.195	0.846	0.002*

Data presented as mean±SD and minimum-maximum. ¹Mann-Whitney U test, ²Kruskal-Wallis test, *p<0.05.
MHLS: Mental Health Literacy Scale, SD: Standard deviation

had diagnosable psychological problems and had low MHL levels (mean MHLS total score: 12). There are other studies that concluded low MHL levels in university students^{17,18}. In the study of Öztaş and Aydoğan¹⁶, in which health professionals evaluated the MHL levels, the mean MHLS score was found to be 17¹⁶. Since the level of knowledge of health professionals is higher than the general population, it is expected that MHL would be higher. In our study, MHL levels were higher in total

(total score: 14) and subscale scores than in the studies of Göktaş et al.¹² and Pehlivan et al.¹⁵, and lower than in the study of Öztaş and Aydoğan¹⁶ considering that the highest score that can be obtained from the MHLS is 22, the MHL level of the participants in our study was slightly above the mid-value.

When the factors affecting MHL were examined, compared to most of the studies in the literature, a lower MHL level was observed with increasing age compared to young adults^{19,20}.

In a review evaluating the studies on MHL in Singapore, the level of MHL was revealed to be generally low, and younger people and those with a better education level were found to have more knowledge and a better understanding of mental disorders than the elderly³. Similarly, our study observed that the MHL level decreased as the age increased. However, it was demonstrated in the literature that different results had been reached regarding the effect of age on MHL^{16,21,22}. In a cross-sectional study examining the MHL status of elderly people in Korea, the participants' self-reported MHL levels were lower in general, while those who were older, had a spouse, and lived in rural areas had lower MHL levels²¹. Piper et al.²² observed that, despite advancing age, elderly people with a mental disorder in one of their relatives had better MHL levels. In this context, it can be considered that having a mental disorder in a relative is a factor that increases the MHL level regardless of age. Öztaş and Aydoğan¹⁶, on the other hand, determined a positive correlation between the ages of the participants and MHL levels in their study on health professionals. In parallel with the advancing age of health professionals, the increase in years in the profession, the increase in professional experience, and the increase in the level of knowledge and awareness about mental health lead to an increase in the level of MHL. In the study in which the MHLS was adapted to the Turkish population, age did not affect the MHL level, unlike the literature¹². Based on all these different results, it was concluded that "age" alone might not affect the MHL level and that other personal characteristics might be more dominant from time to time.

There are different results in the literature regarding the effect of gender on MHL^{12,15,22}. In the study of Pehlivan et al.¹⁵, MHL levels were higher in female university students. The relationship of the male gender with low MHL was also reported by Farrer et al.¹⁹ and Reavley et al.²⁰. Göktaş et al.¹², on the other hand, observed that the gender of university students did not lead to a change in MHL levels. Öztaş and Aydoğan¹⁶ did not find a significant relationship between gender and MHL in healthcare professionals. Piper et al.²² also found no gender difference in MHL levels in older adults. It was concluded that gender differences might vary, especially with age, and become less relevant to MHL as we get older. In our study, no difference was found in terms of MHL levels based on gender. These different results in the literature in terms of gender are considered to be related to the occupational and age differences of the participants included in different studies.

In previous studies, it is observed that the evaluations regarding the effect of marital status on MHL were not performed in detail. In the study of Öztaş and Aydoğan¹⁶, MHL levels of those who were married were high. In our study, although there was no statistically significant difference in terms of marital status and MHLS total score, knowledge and resource subscale MHLS

scores were found to be significantly higher in the married individuals compared to the singles. Although the prediction that marital status will not be a variable that affects MHL is accepted, it is thought that different results may be obtained in different study groups.

Another critical factor affecting MHL is education level. Studies have concluded that high education level positively affects MHL^{20,23,24}. On the other hand, Piper et al.²² did not find a relationship between education level and MHL in the elderly people. Our study's data also revealed a strong correlation between education level and MHL, in line with the majority of the literature. It is thought that the probable reason for the higher MHL level of those with higher education is that they have better psychological awareness and help-seeking knowledge. Low education level leads to inadequacy in understanding mental disorders, suggesting a need for education and interventions for the general population.

Several studies have examined the effect of people's having a diagnosed or undiagnosed mental health disorder on MHL^{15,18,21,24}. In a study performed with cancer patients in 2019, the severity of depression and anxiety symptoms in people with and without a history of cancer was investigated, and MHL levels were evaluated in terms of major depressive disorder and generalized anxiety disorder. In this study, patients with cancer had lower MHL levels than healthy controls, and it was not associated with anxiety and depression symptoms²⁴. Similarly, Pehlivan et al.¹⁵ did not determine a significant difference between university students with and without a diagnosis of psychiatric illness in terms of MHL. Gorczynski et al.¹⁸, on the other hand, indicated moderate and severe psychological distress in the majority of university students and found low MHL levels. A study performed with the geriatric population determined that the presence of depression negatively affected MHL²¹. Our study observed that the mean values in the evaluation of anxiety and depression symptoms were below the cut-off values determined for HADS. As anxiety and depression symptoms increased, MHL decreased statistically significantly. Although different results have been obtained in different studies according to the sociodemographic characteristics of the groups studied, the evaluation of MHL levels of people at risk of a mental health disorder is critical in accelerating the diagnosis and treatment process.

Study Limitations

The study's main limitation was that it used face-to-face self-report questionnaires, which might be subject to individual bias. The strength of the study was its prospective setting, and that there are very few similar studies examining this issue in the Turkish population.

CONCLUSION

This study determined that the MHL level was negatively affected by advanced age and the presence of chronic diseases, and it was higher in those with higher education levels, those who were married, and those who worked in any job. For mental health disorders, it is essential to make various interventions on a community basis and individually. With more frequent and effective implementation of training programs to increase the level of MHL, more positive results regarding health and social aspects may be obtained, individuals can better manage their own and their relatives' mental health, and thus the burden of disease can be reduced.

Acknowledgment

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Ethics

Ethics Committee Approval: The study were approved by the Gaziosmanpaşa Training and Research Hospital Local Ethics Committee (approval no: 371, dated: 24.11.2021).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T.K., Ç.A., O.B., Concept: S.T.K., Ç.A., O.B., Design: S.T.K., Ç.A., O.B., Data Collection or Processing: S.T.K., Ç.A., O.B., Analysis or Interpretation: S.T.K., Ç.A., O.B., Literature Search: S.T.K., O.B., Writing: S.T.K., Ç.A., O.B.

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The Effects of Exercise on Health Belief and Health Anxiety

Egzersiziz Sağlıklı Olma İnancı ve Sağlık Anksiyetesi Üzerindeki Etkileri

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ABSTRACT

Aim: The aim of this study is to examine the effects of exercise on the beliefs of being healthy and anxiety for their health.

Materials and Methods: This study was planned as a single-center, cross-sectional study. The population of the study consisted of patients who applied to the Family Medicine Polyclinic. The study was conducted with 331 healthy volunteers and the sociodemographic data and health status of each participant were questioned by face-to-face interview technique using the Demographic Information Form prepared by us. Participants' Exercise Health Belief Model Scale (EHBMS) and Health Anxiety Scale to measure the presence of anxiety were applied and recorded.

Results: In the study conducted with a total of 339 subjects, 175 (51.6%) of whom were women, 67.3% of the subjects were exercising. While 23.9% of those who were exercising were doing it every day, 28.9% were doing 1-2 times a week. Participants' EHBMS mean score was 76.88±12.45, and Health Anxiety Scale mean score was 22.11±11.97. It was found that regular exercise was positively correlated with general health perception and negatively correlated with health anxiety.

Conclusion: In our study, it was concluded that individuals who exercised had lower anxiety levels and felt healthier. All individuals should be advised to engage in physical activity considering their ages.

Keywords: Exercise, health anxiety inventory, Exercise Health Belief Model Scale

ÖZ

Amaç: Bu çalışmanın amacı egzersiz yapan bireylerin sağlık ve anksiyete durumları üzerindeki etkisini incelemektir.

Gereç ve Yöntem: Bu çalışma tek merkezli, kesitsel bir araştırma olarak planlandı. Araştırmanın evrenini Aile Hekimliği Polikliniği'ne başvuran hastalar oluşturdu. Çalışma 331 sağlıklı gönüllü ile yapıldı ve her katılımcının sosyodemografik verileri, sağlık durumları tarafımızca hazırlanan Demografik Bilgiler Formu kullanılarak yüz yüze görüşme tekniği ile sorgulandı. Katılımcıların Egzersiz Sağlık İnancı Modeli Ölçeği (ESİMÖ), anksiyete varlığını ölçmek için Sağlık Anksiyetesi Ölçeği uygulandı ve kayıt altına alındı.

Bulgular: Yüz yetmiş beşi (%51,6) kadın olmak üzere toplam 339 olgu ile yapılan çalışmada, olguların %67,3'ü egzersiz yapmaktaydı. Bu olgulardan %23,9'u her gün egzersiz yaparken, %28,9'u haftada 1-2 kez egzersiz yapıyordu. Katılımcıların ESİMÖ puan ortalaması 76,88±12,45 idi ve Sağlık Anksiyetesi Ölçeği puanı ortalaması 22,11±11,97 idi. Düzenli egzersiz, genel sağlık algısı ile pozitif yönde, sağlık anksiyetesi ile negatif yönde anlamlı ilişkisi bulundu.

Sonuç: Çalışmamızda; egzersiz yapan bireylerin, anksiyete düzeylerinin daha düşük olduğu ve kendilerini daha sağlıklı hissettikleri sonucu ortaya çıkmıştır. Tüm bireylere yaşına uygun fiziksel aktivitede bulunmaları önerilmektedir.

Anahtar Kelimeler: Egzersiz, sağlık anksiyetesi envanteri, Egzersiz Sağlık İnancı Modeli Ölçeği

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INTRODUCTION

Physical activity is one of the essential elements of a healthy life. Age-appropriate and regular physical activity provides physical, mental and social benefits to all individuals. Regular exercise both protects physical health and provides benefits for the individual in areas such as weight control, substance abuse, social cohesion and socialization, which are important for a healthy life¹.

As a result of increasing transportation opportunities, accelerating technological developments and increasing urbanization, physical mobility has decreased to 20% in some societies. According to the data of the World Health Organization, lack of physical activity, also defined as physical inactivity, ranks 4th among the "Global Mortality Risk Factors". It has been observed that physical inactivity is the basis of many chronic diseases^{2,3}.

Regular physical activity significantly reduces the risk of developing cardiovascular diseases such as cerebrovascular accident, myocardial infarction and heart failure. In addition, it has been found to have positive effects on the prognosis of hypertension, dyslipidemia and muscle and joint diseases⁴.

It has been reported that regular walking programs significantly reduce depression, anxiety and stress in patients with generalized anxiety disorder, panic disorder and social phobia⁵.

Sleep and circadian rhythm are also regulated by exercise⁶. It has been shown that regular exercise increases sleep quality along with melatonin secretion⁷.

It is recommended that children aged 6-17 do 60 minutes of moderate physical activity per day, and that individuals aged 18-64 should do at least 150 minutes of moderate-paced physical activity or at least 75 minutes of vigorous physical activity throughout the week⁸.

It is inevitable for individuals to seek health when they are sick. It is very important to protect and improve the health of the individual before he becomes ill. In addition to environmental factors, the individual's own attitudes and behaviors are also important in the health status of individuals. Behaviors and attitudes of individuals have an important place in protecting and reinforcing their health, and in their belief and desire for treatment⁹.

Educational status, economic status and awareness level of individuals are the determining factors for health seeking. In addition, they must have a healthy psychology.

Regular physical activity not only contributes to significant reductions in mortality and morbidity rates, but also contributes to individuals' mood, general well-being, and the formation of a healthy society^{10,11}.

This study aims to examine the relationship between exercise status and belief in being healthy and health anxiety level.

MATERIALS AND METHODS

Technical Information

This study was planned as a single-center, cross-sectional study. The sample size was calculated using the simple random sampling method from the study population, and the number of volunteers required to participate in the study was calculated as 331, when 2400 people over the age of 18 without chronic diseases were accepted as the population. This study was conducted with 331 healthy volunteers who applied to the Family Medicine outpatient clinic between 01 December 2020 and 01 February 2021, meeting the inclusion criteria and willing to participate in the study. Informed consent was obtained from the participants, and then the demographic information form including age, gender, marital status, education level, income level and exercise frequency of each participant was applied by face-to-face interview technique. Participants' Exercise Health Belief Model Scale (EHBMS) and Health Anxiety Scale to measure the presence of anxiety were applied and recorded. Ethics committee approval of the study was given by the Ministry of Health Istanbul Provincial Health Directorate Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (decision no: 161, date: 23.09.2020).

Statistical Analysis

For the purpose of evaluating the findings obtained in the study, IBM Statistical Package for the Social Sciences (SPSS) statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis. In the analysis of the study data, the conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilks test. In addition to descriptive statistical methods (mean, standard deviation, frequency), the Kruskal-Wallis test was used for the comparison of the parameters that did not show normal distribution in the comparison of quantitative data, and the Dunn's test was used to determine the group that caused the difference. The Mann-Whitney U test was used for the comparison between two groups of parameters that did not show normal distribution. The Spearman's rho correlation analysis was used to examine the relationships between parameters that did not conform to the normal distribution.

RESULTS

The ages of the participants in our study ranged from 18 to 74 years, with a mean age of 36.99 ± 11.28 years and a median of 34 years. 51.6% of the cases were female. It was determined that 78.8% of the participants had high school or higher

education, and 51.3% of them had a working period of 3-5 years. The sociodemographic data of the participants in the study are given in Table 1.

When the ages of the participants are evaluated; it was determined that there was a 13.7% significant relationship between exercise and reducing individual health expenses as the age increased. There was a significant positive correlation of 22.9% between the age of the participants and the level of anxiety they felt for their health ($p=0.000$). The relationship between the ages of the participants and their anxiety levels is given in Table 2.

When the working time was compared, a significant relationship was found between the exercise they did and the expectation that it would contribute positively to their health in those who had a working period of 1-3 years ($p_1=0.031$, $p_2=0.027$, respectively). The correlation between the working time and the sub-dimensions of the scales is given in Table 3.

Table 1. Information on sociodemographic data			
		Min-Max	Mean $\pm$ SD (median)
Age (year)		18-74	36.99 $\pm$ 11.28 (34)
		n	%
Gender	Female	175	51.6
	Male	164	48.4
Marital status	Married	256	75.5
	Single	83	24.5
Educational status	Primary school	72	21.2
	High school or higher education level	267	78.8
Duration of work life	1-3 years	81	23.9
	3-5 years	174	51.3
	5-10 years	1	0.3
	Over 10 years	83	24.5
Income status	Normal	125	36.9
	High income	214	63.1
Exercise status	Yes	228	67.3
	No	111	32.7
Frequency of exercise	Regular-every day	81	23.9
	1-2 times a week	98	28.9
	Irregular	55	16.2
	Other	105	31

EHBMS: Exercise Health Belief Model Scale, SD: Standard deviation, Min-Max: Minimum-maximum

The level of anxiety about health status of individuals with only primary education was found to be significantly higher than those with high school or higher education ($p=0.040$). The correlation between the education level of the participants and the scales is given in Table 4.

67.3% of the participants were exercisers. Of the group that exercised, 23.9% exercised every day, 28.9% exercised 1-2 times a week, and 16.2% at irregular intervals (Table 5).

The well-being of those who exercised regularly every day was found to be significantly higher than those who exercised at other frequencies ($p=0.000$). It was determined that those who exercised at least 2 days a week had less anxiety about their health compared to the other groups ($p=0.000$). It was observed that there was a negative significant relationship between the anxiety levels of individuals and their health status ($p=0.000$).

It was determined that individuals who did not exercise were hypersensitive to changes in their bodies and their anxiety levels were significantly higher than the other groups. This situation was found to be similar in those who exercised irregularly ($p_1=0.000$, $p_2=0.000$, $p_3=0.000$ respectively). The correlation between the frequency of exercise and the scales is given in Table 6.

DISCUSSION

In this study, which examined the relationship between the effects of physical activity on health and the anxiety levels of individuals, it was seen that those who exercised evaluated their own health more positively. It was also found that their anxiety levels were low. Since the results obtained with the EHBMS, which is a quick and practical test to be administered

Table 2. Evaluation of the correlation between age and sub-dimensions of the scale		
Age		
	r	p
EHBMS		
General health	-0.058	0.290
Severity	-0.077	0.157
Threat	-0.102	0.061
Benefit cost	-0.137	0.012
Drawbacks of not doing	0.177	0.001
Total EHBMS score	-0.053	0.329
Health Anxiety Score		
Hypersensitivity to physical symptoms and anxiety score	0.210	0.000
Disease adverse outcomes score	0.253	0.000
Health anxiety total score	0.229	0.000

EHBMS: Exercise Health Belief Model Scale

Table 3. Evaluation of the sub-dimensions of the scale according to working duration

	Working duration			p
	1-3 years	3-5 years	Over 5 years	
	Mean±SD (median)	Mean±SD (median)	Mean±SD (median)	
EHBMS				
General health	9.48±3.16 (9)	8.87±2.58 (9)	8.89±2.85 (9)	0.285
Severity	10.23±3.16 (10)	9.75±2.98 (10)	9.61±3.38 (10)	0.428
Threat	24.28±6.01 (25)	22.51±5.47 (23)	22.79±5.82 (23)	0.061
Benefit cost	21.46±4.01 (21)	20.33±4.31 (21)	19.92±5.08 (20)	0.079
Drawbacks of not doing	14.44±5.24 (14)	14.67±5.53 (14)	14.29±5.8 (13)	0.735
Total EHBMS score	79.9±12.84 (79)	76.14±12.03 (76)	75.49±12.6 (75)	0.049
Health Anxiety Score				
Hypersensitivity to physical symptoms and anxiety score	17.54±9.28 (15)	16.91±9.7 (14)	18.71±10.68 (15.5)	0.356
Disease adverse outcomes score	4.62±2.83 (4)	4.47±2.67 (4)	4.86±3.09 (4)	0.783
Health anxiety total score	22.16±11.5 (20)	21.37±11.62 (17)	23.57±13.1 (22)	0.438

EHBMS: Exercise Health Belief Model Scale, SD: Standard deviation

Table 4. Evaluation of scale sub-dimensions according to education level

Education level	Primary education	High school and higher education	p
	Mean±SD (median)	Mean±SD (median)	
EHBMS			
General health	9.24±2.89 (9)	8.97±2.78 (9)	0.303
Severity	10.25±3.05 (10.5)	9.72±3.14 (10)	0.193
Threat	24±5.83 (25)	22.73±5.67 (23)	0.069
Benefit cost	20.71±5.31 (21.5)	20.44±4.22 (21)	0.402
Drawbacks of not doing	15.81±6.26 (15.5)	14.18±5.26 (13)	0.075
Total EHBMS score	80±13.37 (81.5)	76.03±12.08 (76)	0.006
Health Anxiety Score			
Hypersensitivity to physical symptoms and anxiety score	19.44±10.29 (18)	16.99±9.69 (14)	0.064
Disease adverse outcomes score	5.22±2.79 (5)	4.43±2.8 (4)	0.024
Health anxiety total score	24.67±12.57 (23)	21.42±11.73 (18)	0.040

EHBMS: Exercise Health Belief Model Scale, SD: Standard deviation

Table 5. Evaluation of sub-dimensions of the scale according to exercise status

Status of doing exercise	Yes	No	p
	Mean±SD (median)	Mean±SD (median)	
EHBMS			
General health	9.47±2.88 (9)	8.11±2.38 (9)	0.000
Severity	10.36±3.11 (11)	8.74±2.88 (9)	0.000
Threat	23.39±6.08 (24)	22.22±4.82 (23)	0.041
Benefit cost	21.04±4.5 (21)	19.38±4.2 (20)	0.003
Drawbacks of not doing	12.09±3.89 (12)	19.51±5 (20)	0.000
Total EHBMS score	76.35±13.24 (76)	77.96±10.65 (78)	0.255
Health Anxiety Scale			
Hypersensitivity to physical symptoms and anxiety score	12.42±5.84 (11)	27.96±7.99 (31)	0.000
Disease adverse outcomes score	3.46±2.11 (3)	6.95±2.62 (7)	0.000
Health anxiety total score	15.87±6.94 (14)	34.91±9.74 (38)	0.000

EHBMS: Exercise Health Belief Model Scale, SD: Standard deviation

Table 6. Evaluation of the sub-dimensions of the scale according to the frequency of exercise

Exercise frequency	Everyday regular	1-2 times a week	Irregular	Other	p
	Mean±SD (median)	Mean±SD (median)	Mean±SD (median)	Mean±SD (median)	
EHBMS					
General Health	9.89±2.43 (9)	9.23±3.25 (9)	9.2±2.65 (9)	8.07±2.41 (9)	0.000
Severity	10.81±2.82 (11)	10.06±3.38 (10)	10.15±2.9 (11)	8.69±2.9 (8)	0.000
Threat	23.7±6.41 (25)	22.91±5.56 (23)	23.47±6.51 (24)	22.3±4.79 (23)	0.188
Benefit cost	21.64±4.59 (21)	20.37±4.12 (20)	21.09±5.02 (22)	19.43±4.17 (20)	0.007
Drawbacks of not doing	11.27±3.76 (10)	12.58±4.04 (12)	13.02±4.48 (12)	19.63±4.82 (20)	0.000
Total EHBMS score	77.32±13.77(78)	75.15±13.05(75)	76.93±12.24 (75)	78.11±10.81 (78)	0.229
Health Anxiety Scale					
Hypersensitivity to physical symptoms and anxiety score	11.23±5.31 (9)	12.11±5.53 (11)	15.78±7.77 (15)	28.29±7.55 (31)	0.000
Disease adverse outcomes score	3±1.8 (3)	3.41±2.05 (3)	4.49±2.74 (4)	7±2.5 (7)	0.000
Health anxiety total score	14.23±6.16 (13)	15.52±6.45 (14)	20.27±9.7 (19)	35.29±9.09 (38)	0.000

EHBMS: Exercise Health Belief Model Scale, SD: Standard deviation

to individuals, were observed to be reliable, it was thought that it should be used more frequently in daily practice.

Increasing physical inactivity in society brings with it many health problems. Physical activity is one of the basic conditions of living a healthy life. In the study of Limaroon et al.¹², in which they used the Health Belief Model (HBM), 17.7% of the participants saw not exercising as a threat to catching a disease, and 75% of the participants stated that they were physically active at least 3 times a week. In our study, 67.3% of the participants engaged in physical activity. Those who did physical activity every day or twice a week were in the majority. Those who exercised were aware that if they did not do regular physical activity, it would pose a risk to their health.

In their cohort study, in which Sanchez-Villegas et al.¹³ evaluated physical activity among university graduates, the level of anxiety for health status of individuals who sat for 42 hours a week was found to be 1.3 times higher than that of individuals who sat for 10 hours. In another study conducted in Austria, the Health Quality of Life Scale and the Workforce Sitting Questionnaire were used, and as a result, it was stated that as the duration of sitting at work increases and accordingly the duration of physical activity decreases, the anxiety level of the participants for their health increases¹⁴. In our study, it was determined that those who exercised were less worried about their health and showed less reaction to the changes in their bodies. It has been observed that a sedentary life both increases anxiety and has negative effects on a healthy body image.

In the study of Pham et al.¹⁵ in Vietnam using the International Short Form of Physical Activity Questionnaire and the Patient Health Questionnaire-9, it was observed that the frequency of depression decreased with regular physical activity, although

not at a significant level. In our study, it was determined that those who do regular physical activity every day worry less about their health and have more positive thoughts about their health than those who do it irregularly. At the same time, it was seen that those who exercised regularly knew the positive effects of this and exercised to create less health expenses throughout their lives.

In a study using the HBM in Thailand, the majority of those who exercise stated that it had positive effects on their social relationships with other people and their health¹². Regular exercise has an important place in preventing many diseases. It is inevitable for individuals who want to lead a healthy life to exercise regularly. In our study, the main purpose of the exercisers was to be protected from diseases and to lead a healthy life. It was found that those who knew that exercise was beneficial were less concerned about their health.

In our study, it was observed that physical activity increased the perception of general health. It was determined that individuals had more positive thoughts about their own health as physical activity increased. With the increasing perception of health, it was concluded that individuals were less worried and faced less obstacles in their bodies.

It was observed that individuals had difficulty in allocating time for physical activity despite knowing the bad consequences of possible diseases when they led a sedentary life. Although people are aware of the negative consequences of a possible disease, it was determined that they could not spare time for physical activity, and this was statistically significant. A positive correlation was found between the reasons for avoiding physical activity and the level of anxiety they felt for their health.

In our study, the mean age was found to be 36.9 years. There is a negative relationship between age and the thought that physical activity provides benefits. Younger participants thought that physical activity would bring more benefits for their health and social purposes. However, in our study, a positive relationship was found between age and the reasons for preventing exercise. The risk of injury and falling while doing physical activity for elderly individuals is one of the main reasons that prevent them from doing physical activity. It was thought that it would be important to build more sheltered areas especially for the elderly and to review these existing areas for all kinds of fall and injury risks.

There are different results in the literature about the correlation between education level and physical activity. The Godin Physical Activity Questionnaire was also used in the study of Avluklu¹⁶ there was no significant correlation between education level and physical activity. In the study of Gedik¹⁷, the Self-Efficacy Questionnaire was used, and it was reported that the rate of doing physical activity increased with the increase in education level. In our study, a negative relationship was found between education level and physical activity. Although the education level was low, it was observed that individuals believed in the importance of exercise.

Health anxiety causes an increase in the severity of physical complaints, leading to repeated applications to health institutions¹⁸. In the study of Gül et al.¹⁹ with the Short Form of Health Anxiety Inventory, the mean total health anxiety score was found to be 17.76 ± 7.0119 . In the study of Yılmaz et al.²⁰, in which they used the Health Anxiety Scale, the mean total health anxiety score of hospitalized patients was determined as 17.34 ± 8.4520 . In our study, it was found that the total mean score of the participants from the Health Anxiety Inventory was 22.11 ± 11.97 . The reason for the high anxiety score in our study was considered to be the socioeconomic levels and living standards of the participants.

There are many studies in the literature investigating the correlation between income status and physical activity. In the study of Farrell and Shields²¹ with 6.467 people in England, a positive relationship was shown between the income level of individuals and their families and physical activity. In the study conducted by Rimal²² with 2.880 families in the USA, a positive relationship was found between income level and spending time for physical activity. In our study, it was seen that the majority of the participants were individuals with a high income level. Individuals with normal income levels were aware that exercise was beneficial for their health, but their thoughts and anxiety about their health were higher than those with higher incomes. Even though individuals with normal incomes interpreted their health status negatively, they knew that they would turn this into a positive direction by engaging in physical activity.

In the literature, there are studies on the reasons that prevent physical activity. In the study of Lovell et al.²³ in which they used the Exercise Benefits/Barriers Scale, it was stated that the biggest obstacle to physical activity was families. In the study of Gyurcsik et al.²⁴, it was stated that reasons such as not having enough time, being associated with social activities, and having a high workload prevented the majority of the participants from doing physical activity. In the study of Kaushal et al.²⁵, using the Health Belief Model, it was shown that the main reasons hindering physical activity were difficulty in allocating time, and the perception of falling, injury and disability. In our study, it was observed that there were more reasons that prevented married individuals from doing physical activity. This was thought to be due to factors such as increased responsibilities and family.

In our study, we examined the level of anxiety about physical activity, belief in being healthy, and health status. In the literature, there is no study in which EHBMS and Health Anxiety Scale are used together. In this study, in which we used the EHBMS and the Health Anxiety Scale, we determined that the state of exercise was positively related to the general health perception and negatively related to the health anxiety. We are of the opinion that exercising has an important role in individuals to lead a healthier life. We think that doing physical activity at regular intervals will make individuals worry less about their health.

Study Limitations

The participants in our study consisted of healthy individuals without acute or chronic diseases. Results of physical activity may differ in studies involving other patient groups.

CONCLUSION

In our study, it was determined that individuals engaged in regular physical activity had a healthier body and had less anxiety. The benefits of physical activity have been demonstrated. Individuals should be encouraged to exercise in order to stay healthy and reduce their anxiety levels.

Ethics

Ethics Committee Approval: This study was approved by the Ministry of Health İstanbul Provincial Health Directorate Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (decision no: 161, date: 23.09.2020).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.A., Concept: R.A., Design: R.A., O.B., Data Collection or Processing: R.A., Analysis or Interpretation: R.A., Literature Search: R.A., O.B., Writing: R.A., O.B.

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The Possible Role of The Long Non-Coding RNA NORAD in Mitomycin C-Related Chemoresistance

Uzun Kodlamayan RNA NORAD'ın Mitomisin C İlişkili Kemorezistansta Olası Rolü

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ABSTRACT

Aim: Non-coding RNA activated by DNA damage (NORAD) is a long non-coding RNA activated during DNA damage response. Accumulating evidence suggest that NORAD is overexpressed in human cancers and associated with the drug-induced chemoresistance. The present study aims to explore the possible role of long non-coding RNA NORAD during mitomycin C-related chemoresistance and mitomycin C-induced DNA damage response.

Materials and Methods: In cell culture experiments, MDA-MB-231 breast cancer cells were used. MTT cell viability assay was used to determine the effects of mitomycin C on breast cancer cells and application dose was determined accordingly. For analysis of NORAD gene expression levels, quantitative real-time polymerase chain reaction method was used.

Results: Mitomycin C was found to suppress cell viability of breast cancer cells in a dose-dependent manner and half-maximal inhibitory concentration was determined as 1.12 µg/mL ($p<0.0001$). Notably, significant differential activation of NORAD was determined in breast cancer cells treated with the mitomycin C ($p<0.0001$).

Conclusion: Findings obtained here strongly suggest that NORAD is possibly involved in mitomycin C-related chemoresistance and mitomycin C-induced DNA damage response.

Keywords: DNA damage, breast cancer, mitomycin C, lncRNA, NORAD

ÖZ

Amaç: Non-coding RNA activated by DNA damage (NORAD), deoksiribo nükleik asit (DNA) hasarı cevabı sırasında aktive olan bir uzun kodlamayan ribonükleik asittir (RNA). Çalışmalar, NORAD'ın insan kanserlerinde aşırı eksprese edildiğini ve ilaca bağlı kemorezistans ile ilişkili olduğunu göstermektedir. Bu çalışma, mitomisin C ile ilişkili kemorezistans ve mitomisin C ile indüklenen DNA hasar yanıtı sırasında spesifik olarak aktive edilen bir uzun kodlamayan RNA NORAD'ın olası rolünü araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Hücre kültürü deneylerinde MDA-MB-231 meme kanseri hücreleri kullanıldı. Mitomisin C'nin meme kanseri hücreleri üzerindeki etkilerini belirlemek için MTT hücre canlılığı testi kullanıldı ve uygulama dozu buna göre belirlendi. NORAD gen ekspresyon düzeylerinin analizi için kantitatif qPCR yöntemi kullanıldı.

Bulgular: Mitomisin C'nin meme kanseri hücrelerinin hücre canlılığını doza bağlı olarak baskıladığı ve yarı-maksimum inhibisyon konsantrasyonunun 1,12 µg/mL olduğu belirlendi ($p<0,0001$). Özellikle, Mitomisin C ile muamele edilen meme kanseri hücrelerinde NORAD'ın önemli bir farklı aktivasyonu belirlendi ($p<0,0001$).

Sonuç: Burada elde edilen bulgular, mitomisin C ile ilişkili kemorezistans ve mitomisin C ile indüklenen DNA hasar yanıtında NORAD'ın olası rolünün olabileceğini göstermektedir.

Anahtar Kelimeler: DNA hasarı, meme kanseri, mitomisin C, lncRNA, NORAD

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INTRODUCTION

Although the human genome harbors hundreds of long non-coding ribonucleic acid (RNAs) (lncRNAs), only about a dozen with distinct biological activities and biochemical processes have been identified. Non-coding RNA activated by deoxyribonucleic acid (DNA) damage (NORAD, formerly known as LINC00657), a particular lncRNA transcript which is stimulated in response to DNA injury, has been reported to be necessary for the maintenance of genome integrity¹. Deletion of NORAD leads to chromosomal instability and aneuploidy². NORAD is abundantly expressed in various human cell lines and tissues. Compared to other lncRNAs in mammals, NORAD is highly conserved^{2,3}. NORAD has been discovered to engage with the proteins that regulate DNA replication and repair mechanisms and translocate to the nucleus when stimulated by DNA damage or replication stress^{2,3}. NORAD interacts with RBMX, a DNA damage response component, and prevents RNA-binding motif protein, X-linked (RBMX) from assembling at NORAD-activated ribonucleo protein complex 1. NORAD- or RBMX-depleted cells exhibited a higher incidence of chromosomal segregation abnormalities, slower replication fork speed and deregulation of cell cycle progression². Moreover, studies suggest that NORAD is deregulated in breast, ovarian, cervical, gastric, colorectal, bladder, pancreatic, hepatocellular, esophageal, prostate, lung, thyroid, retinoblastoma, and neuroblastoma cancers⁴. Specifically, overexpression of NORAD stimulates proliferation, invasion, and metastasis of cancerous cells and prevents apoptosis⁴. In addition, several lines of evidence suggest that NORAD is associated with chemoresistance to currently available chemotherapeutic agents such as doxorubicin, gemcitabine, and 5-fluorouracil. In neuroblastoma, it has been shown that increased expression of NORAD is enhanced proliferation, metastasis, and doxorubicin resistance and while interfering with the apoptotic death of neuroblastoma cells by inducing HDAC8 expression through sponging miR-144-3p⁵. Also, NORAD has been reported to act as a competing endogenous RNA (ceRNA) to mediate gemcitabine chemoresistance in bladder cancer through regulating WEE1 expression via sponging miR-155-5p⁶. Also, differential activation of NORAD has shown to be associated with the 5-fluorouracil chemoresistance during hypoxia by acting as a ceRNA by sponging miR-495-3p/HIF-1 α expression in colorectal cancer⁷.

Mitomycin C is a naturally occurring anticancer antibiotic substance derived from streptomyces caespitosus and other streptomyces species. Mitomycin C was discovered in the 1950s by Japanese microbiologists. Mitomycin C is one of the few antibiotics known to react with DNA⁸. It induces DNA damage by introducing monofunctional and bifunctional DNA cross-links. As a prodrug, mitomycin C itself remains inactivated and does not react with DNA and requires bioactivation⁹. The reduction

of the quinone ring, which transforms mitomycin c into a highly reactive unstable alkylating species, is required for DNA crosslinking and alkylating activities¹⁰. Mitomycin C is widely used for the treatment of several human malignancies because of its ability to suppress DNA replication and cell division. It has been shown to be an effective antitumor agent in several cancers, including breast cancer, cervical cancer, non-small cell lung cancer, pancreatic cancer, gastric cancer, prostate cancer, and bladder cancer. Mitomycin C is characterized by its high bio-reductive alkylation under hypoxic conditions. Inside solid tumors, oxygen-deprived cells form an environment in which mitomycin c is highly active¹¹.

Although the molecular mechanism underlying the biological and pharmacological properties of mitomycin C is well characterized, its effect on non-coding RNAs activated during the DNA damage response has not yet been described. Accordingly, in this study, we sought to explore the possible role of NORAD, a lncRNA specifically activated during DNA damage response, during mitomycin C-related chemoresistance and mitomycin C-induced DNA damage response.

MATERIALS AND METHODS

Cell Lines, Culture Conditions, and Chemicals

For the study, HTB-26 (MDA-MB-231) triple negative breast adenocarcinoma cells were obtained from ATCC and propagated using DMEM medium (Cat. No.: D6429, Sigma-Aldrich) complemented with the 1% penicillin/streptomycin and 10% fetal calf serum solution (Cat. No.: A4766801, Sigma-Aldrich). Cell cultures were maintained in moistened carbon dioxide incubator at 37 °C. Mitomycin C isolated from Streptomyces caespitosus was commercially obtained from Sigma-Aldrich (Cat. No.: M4287). 2 mg of mitomycin C was suspended in 10 mL ddH₂O to obtain a stock solution of 200 μ g/mL.

MTT Analysis

Cells were seeded at a concentration of 3x10⁴ cells/mL in 96-well plates and incubated overnight to determine cell viability. Following overnight incubation, cells were treated with the various concentrations of mitomycin C ranging from 0.125 to 2 μ g/mL and incubated for 24 hours. Then, supernatants were discarded, and cells were washed several times with the 1 X PBS solution and subsequently incubated with the 1 mg/mL of MTT (3- (4,5-dimethylthiazol-2-yl) 2,5-diphenyltetrazolium bromide) solution for 40-60 minutes at 37 °C.

Gene Expression Analysis

To investigate the effects of mitomycin C on NORAD expression levels, cells were plated to 12-well culture dishes and incubated overnight to allow attachment. Subsequently, cells were treated with the mitomycin C and incubated for

24 hours. Cells were then harvested using Trypsin-EDTA solution, and RNA purifications were made using GeneJET RNA Purification Kit (Cat. No.: K0702, Thermo Scientific, Waltham, MA, USA) according to the recommendations provided by the manufacturer. RNA quality and concentrations were determined with the help of Thermo Scientific Multiskan GO instrument. The RevertAid First Strand cDNA Synthesis Kit (Cat. No.: FERK1622, Thermo Scientific, Waltham, MA, USA) was used for reverse transcription of RNA samples into cDNA samples. GAPDH and NORAD-specific gene expression PCR primers were designed with the help of NCBI primer blast. Primer pairs for GAPDH were Forward: 5'-AGACCACAGTCCATGCCATCAC-3', Reverse: 5'-GGTCCACCACCCTGTTGCTGT-3' and primer pairs for NORAD were Forward: 5'-CAGAGGAGGTATGCAGGGAG-3', Reverse: 5'-CCACCATCCCCGTGACTAAG-3'. Lastly, to assess gene expression levels of NORAD and GAPDH genes, RealQ Plus 2x Master Mix Green (Cat. No.: A323402, Ampliqon) was used and Rotor-Gene Q real-time PCR instrument was used to perform reactions. Briefly, 12.5 µl RealQ Plus 2x Master Mix, 0.5 µl from each primer (10 µM), 2 µl cDNA and 9.5 µl PCR-grade H₂O were mixed and subjected to following thermal conditions; 15 minutes at 95 °C, 40 cycles of 15 s at 94 °C, 30 s at 60 °C, and 30 s at 70 °C. At the end of each reaction, a melting curve analysis was performed between 72 °C and 95 °C.

Statistical Analysis

For the calculation of relative gene expression levels, $2^{-\Delta Ct}$ formula was used. GAPDH was used as a reference gene for calculations. All experiments were performed in triplicate. Statistical examination of the obtained data was achieved using GraphPad Prism 9 software, with p values less than 0.05 accepted as significant. For comparisons between two independent groups, the Student's t-test was used whereas variance analysis was used for comparisons of more than two groups.

RESULTS

Cell Viability of Cells Upon Mitomycin C Treatments

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer with no effective therapy at present. To explore mitomycin C-related chemoresistance in breast cancer, MDA-MB-231 TNBC was used. Accordingly, MTT assay was used to examine the effect of mitomycin C on viability of breast cancer cells, and cells were treated with the varying concentrations of mitomycin C. Remarkably, the viability of breast cancer cells was found to be dramatically decreased in a dose-dependent manner (Figure 1). Half-maximal inhibitory concentration (IC₅₀) of mitomycin C against MDA-MB-231 breast cancer cells was calculated as 1.12 µg/mL. Treatment with 0.125 µg/mL, 0.25 µg/mL, 0.5 µg/mL, 1 µg/mL and 2 µg/mL mitomycin C for 24 h resulted in 68.72%, 60.86%, 53.20%, 49.27%, and

35.20% cell viability, respectively, compared to the control group (Figure 1). Significant inhibition of cell viability was observed at 1 µg/mL (p<0.0001) and 2 µg/mL (p<0.0001) doses of mitomycin C compared to the untreated group.

Differential Activation of NORAD Upon Mitomycin C Treatments

To further test the influence of mitomycin C on the expression of NORAD lncRNA, we have performed gene expression analysis upon mitomycin C treatments in breast cancer cells. Notably, NORAD expression levels were determined to be significantly enhanced in cells treated with the 1 µg/mL and 2 µg/mL mitomycin C (p<0.0001). Fold-change analysis revealed that expression of NORAD was increased 5.7-fold and 5.2-fold in cells treated with the 1 µg/mL and 2 µg/mL mitomycin C, respectively (Figure 2), strongly indicating that treatment with mitomycin C induces DNA damage response involving NORAD lncRNA.

DISCUSSION

The main goal of cancer treatment is surgical removal of tumor cells or their destruction by radiation or chemotherapy. Therefore, understanding drug-induced genetic alterations and chemoresistance is of great importance for improving patient outcomes in cancer chemotherapy. The poor success of cancer chemotherapy is often due to adverse effects and resistance to chemotherapeutic agents¹². There is increasing evidence that an optimal level of DNA repair is essential for the elimination of mutations and DNA lesions to prevent malignant transformation¹². Thus, DNA repair function emerges as a double-edged sword in cancer treatment. While a low level of DNA repair activity sensitizes cancer cells to chemo-mediated killing, it also allows a second primary tumor to develop¹². In contrast, overactivity of DNA repair functions promotes cancer progression. Maintenance of the genome integrity by DNA damage response and repair mechanisms ensures genomic stability and keeps chromosome number constant. Moreover, lncRNA NORAD is a specific non-coding RNA molecule triggered in response to DNA injury. More recently, NORAD has shown to interact with proteins of DNA replication and repair machinery and migrates to the nucleus in case of stress conditions. NORAD has also been shown to be essential for the assembly of a topoisomerase complex, called NARC1, which is critical for the maintenance of genome stability. NORAD was also shown to sequester PUMILIO proteins to preserve genome integrity^{1,13,14}. Although NORAD is critical for genomic stability, it has been reported to be a crucial oncogenic driver in human cancers. High activity of NORAD was associated with increased cell proliferation and aggressiveness of human cancers. NORAD was reported to be markedly overexpressed in gastric cancer tissue compared to adjacent healthy tissue.

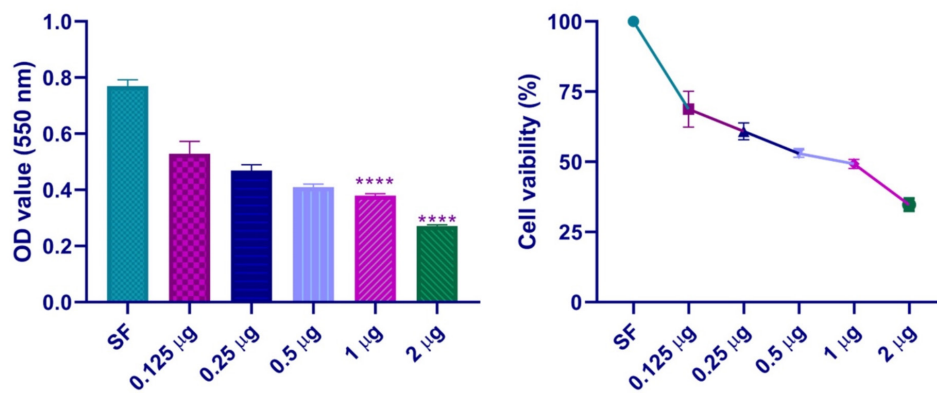


Figure 1. Dose-dependent inhibition of cell viability of MDA-MB-231 breast cancer cells treated with different concentrations of mitomycin C

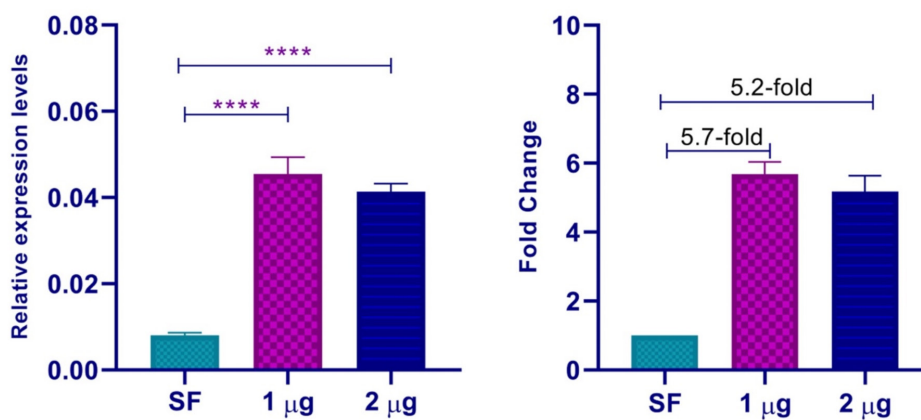


Figure 2. The effect of mitomycin C treatments on NORAD expression levels. NORAD was determined to be differentially activated in response to mitomycin C treatments

NORAD: Non-coding RNA activated by DNA damage

Inhibition of NORAD expression reduced cell viability and migration and promoted apoptotic death of gastric cancer cells by inducing the expression of E-cadherin Bax, and PTEN, and downregulating Bcl-2 proteins¹⁵. NORAD was also determined to be overexpressed in oral squamous cell carcinoma tissues and cell lines, and it functions as a tumor promoter to enhance the advancement of oral squamous cell carcinoma by sponging miR-577¹⁶. Similarly, higher expression of NORAD was found in cancerous tissues of thyroid carcinoma patients, and ectopic overexpression of NORAD was associated with increased cell proliferation, invasion, and migration and activated epithelial-to-mesenchymal transition (EMT) by inhibiting miR-202-5p¹⁷. Knockdown of NORAD was also discovered to be associated with the inhibition of EMT of head and neck cancer stem cells through regulating miR-26a-5p¹⁸. Significant overexpression

of NORAD was also found in osteosarcoma tumors and was associated with the clinic and pathological findings of patients, such as tumor size, grade and metastasis¹⁹. Although limited, a relationship between NORAD and resistance to certain types of chemotherapeutic agents has also been demonstrated. Particularly, NORAD has been linked to gemcitabine resistance in bladder cancer by acting as a competitive endogenous RNA that inhibits miR-155-5p activity. Silencing of NORAD in gemcitabine-resistant bladder cancer cells impairs proliferation and cell cycle progression and induces apoptosis via regulation of the miR-155-5p/WEE1 axis⁶. In addition, NORAD was shown to be associated with the hypoxia-induced 5-fluorouracil chemoresistance in colorectal cancer⁷. Consistent with all these observations, in the present study, it has been shown that NORAD was significantly activated in response to mitomycin

C treatment in breast cancer cells, suggesting that NORAD may be related to mitomycin C resistance at the organism level. NORAD inhibitory therapy in combination with mitomycin C chemotherapy could be a good treatment method for triple negative breast cancer. Overall, the strong tumor-promoting function and association with chemoresistance to certain drugs also support a role for NORAD in chemoresistance to mitomycin C.

Study Limitations

While this study successfully evaluated the role of NORAD in mitomycin C-related chemoresistance and mitomycin C-induced DNA damage response, there were some limitations. In the future studies, gain of function and loss of function experiments of NORAD along with the mitomycin treatments are of great interest to understand more about the role of NORAD during DNA damage response and repair.

CONCLUSION

In conclusion, we describe here that lncRNA NORAD was activated in response to mitomycin C treatments in TNBC cells, strongly indicating that NORAD may relate to the mitomycin C-related chemoresistance. However, these findings need to be supported by additional comprehensive studies.

Ethics

Ethics Committee Approval: The study was performed in cancer cell lines; therefore, ethical approval was not required.

Informed Consent: Not applicable for the present study.

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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Effectiveness of the Trimester MPV/Platelet and PDW/Platelet Ratios in Predicting Abortus Imminens and Abortion

Birinci Trimester MPV/Trombosit ve PDW/Trombosit Oranlarının Abortus Imminens ve Abortusu Öngörmede Etkinliği

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ABSTRACT

Aim: The aim of this study is to examine the role of platelet value, mean platelet volume (MPV) value, platelet distribution width (PDW) value, MPV/platelet ratio and PDW/platelet ratio in predicting abortus imminens and abortion that may occur during pregnancy.

Materials and Methods: Our study was conducted between the years of 2018 and 2020 and 300 pregnant women between the 6th and 12th gestational weeks, who were admitted to obstetrics outpatient clinics and gave complete blood count test, were included in the study. The patients' ages, number of abortion, gestational weeks, platelet values, MPV values, PDW values, MPV/platelet ratios and PDW/platelet ratios were recorded from the patient files. Patients were divided into 3 groups; abortion, abortus imminens and control groups. All data were analyzed comparatively.

Results: There was no significant difference ($p>0.05$) among the abortion group, the abortus imminens group and the control group in terms of platelet values, PDW values, MPV values, PDW/platelet ratios and MPV/platelet ratios. When evaluated in terms of laboratory parameters, the mean platelet value was found as 256.7 ± 65.6 , the PDW value as 12.2 ± 1.8 , the MPV value as 10.2 ± 0.8 , the MPV/platelet ratio as 0.042 ± 0.011 , and the PDW/platelet ratio as 0.051 ± 0.016 .

Conclusion: MPV, PDW and MPV/platelet and PDW/platelet ratios obtained from the complete blood count tests of healthy pregnant women in the first trimester are not effective in predicting the risk of further abortion and abortus imminens.

Keywords: Abortion, abortus imminens, mean platelet volume, platelet, platelet distribution

ÖZ

Amaç: Bu çalışmanın amacı, gebelerde birinci trimester döneminde yapılan rutin tam kan sayımı ile elde edilen trombosit değeri, ortalama trombosit hacmi (MPV) değeri, platelet dağılım genişliği (PDW) değeri, MPV/trombosit oranı ve PDW/trombosit oranının gebelik süresince oluşabilecek abortus imminens ve abortus durumlarını öngörmedeki rolünü incelemektir.

Gereç ve Yöntem: Çalışmaya gebe polikliniklerinde 2018-2020 yılları arasında gebeliğin 6.-12. haftaları arasında tam kan sayımı örneği veren 300 hasta alındı. Hasta dosyalarından hastaların yaşları, abortus sayıları, gebelik haftaları, trombosit değerleri, MPV değerleri, PDW değerleri, MPV/trombosit oranları ve PDW/trombosit oranları kaydedildi. Hastalar düşük, düşük tehdidi ve kontrol olmak üzere 3 gruba ayrıldı. Tüm veriler karşılaştırmalı olarak analiz edildi.

Bulgular: Abortus grubu, abortus imminens grubu ve kontrol grubu arasında trombosit değerleri, PDW değerleri, MPV değerleri, PDW/trombosit oranları ve MPV/trombosit oranları açısından anlamlı ($p>0,05$) bir farklılık gösterilmemiştir. Laboratuvar parametreleri açısından değerlendirildiğinde ise ortalama trombosit değeri $256,7\pm65,6$, PDW değeri $12,2\pm1,8$, MPV değeri $10,2\pm0,8$, MPV/trombosit oranı $0,042\pm0,011$ ve PDW/trombosit oranı $0,051\pm0,016$ olarak saptanmıştır.

Sonuç: Birinci trimesterde sağlıklı gebelerin tam kan sayımı testinden elde edilen MPV, PDW ile MPV/trombosit ve PDW/trombosit oranları ileri dönem abortus ve abortus imminens riskini öngörmede etkin değildir.

Anahtar Kelimeler: Abortus, abortus imminens, ortalama trombosit hacmi, trombosit, trombosit dağılım genişliği

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INTRODUCTION

Vaginal bleeding is observed in approximately 7% to 27% of first trimester pregnancies, and the rate of abortion in pregnancies in this period is approximately 12%¹. The etiologies of first trimester vaginal bleeding include abortus imminens, abortion, early pregnancy loss and ectopic pregnancy. Physical examination, laboratory tests and ultrasonographic imaging can be used to find the cause of first trimester bleeding and to provide appropriate treatment.

Abortus imminens can be defined as visible vaginal bleeding in which fetal heartbeat is observed but not accompanied by cervical dilatation². Abortion is the most common gynecological emergency seen in approximately 15-20% of imminens pregnancies³. Abortion is pregnancy loss that occurs before 20 weeks. Early abortion refers to intrauterine pregnancies without fetal cardiac activity in pregnancies less than 13 weeks⁴. Known risk factors for abortion include genetic anomalies, maternal age (>35 years), high body mass index, low body mass index (<20 kg/m²), history of previous abortion, history of ectopic pregnancy, smoking, alcohol use, and cardiovascular diseases⁵⁻⁷.

Many biochemical markers have been investigated in order to determine whether abortion or abortus imminens will be observed in the later stages of pregnancy. Among these, the most frequently examined biochemical markers are; serum beta human chorionic gonadotropin (beta HCG), progesterone, estradiol, pregnancy-associated plasma protein A, cancer antigen 125, human placental lactogen, alpha feto-protein, inhibin A is follistatin and activin A⁸. Despite all the researches, since the underlying mechanisms are still not fully known, findings that can predict abortion imminence and abortion could not be obtained.

Prothrombotic events in pregnancy can change the hemostatic balance in the placental vessels. It is thought that abnormal hemostatic response may play a role in the etiology of abortion cases⁹. Many parameters such as mean platelet volume (MPV), platelet distribution width (PDW), MPV/platelet count ratio (MPR) and PDW/platelet count ratio (PPR) are used in the examination of thromboembolic events.

The aim of this study is to examine the role of MPV value, PDW value, MPR ratio and PPR ratio obtained by routine complete blood count in pregnant women in the first trimester in predicting possible abortion and abortus imminens risk.

MATERIALS AND METHODS

After obtaining ethics committee approval for the study Maltepe University Clinical Research Ethics Committee (decision number: 2020/900/48, date: 17.06.2020), archive files and digital media data of each patient were reviewed retrospectively. Pregnant women who applied to the pregnant

outpatient clinics between 2018 and 2020 were included in our study. Patients' ages, abortion numbers, weeks of gestation, platelet values, MPV values and PDW values were recorded from patient files and data.

Women who gave complete blood count samples in their routine check-ups between 6th and 12th weeks of their pregnancy were included in the study. When calculating the gestational week, the gestational week calculated according to the crown-rump length measurement in the first ultrasonography of the patient was taken as basis.

Those who had vaginal bleeding at the time of admission, pregnant women older than 45 years, ectopic, multiple and molar pregnancies, those with thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura and essential thrombocytosis, hypersplenism and hereditary thrombocytopenia, and those with a history of drug use that may affect platelet functions were not included. In addition, patients with missing data or follow-up were excluded from the study.

Statistical Analysis

Mean, standard deviation, median minimum and maximum values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. ANOVA, Kruskal-Wallis, and Mann-Whitney U tests were used in the analysis of quantitative independent data. Analyzes were performed using the Statistical Package for the Social Sciences 27.0 statistical program.

RESULTS

A total of 300 people, including 100 women who had abortion, 100 pregnant women with abortus imminens diagnosis, and 100 healthy women who reached the birth week without abortus imminens diagnosis as the control group, were included in the study. The mean age of the patients was 33.0±4.9 (21-45) years. The mean gestational week of the women included in the study was determined as 8.1±1.6. When all three groups were examined, the patients' ages, weeks of gestation and number of abortions were similar ($p>0.05$) (Table 1).

When evaluated in terms of laboratory parameters, mean platelet value of all pregnant women included in the study was 256.7±65.6, PDW value was 12.2±1.8, MPV value was 10.2±0.8, MPR rate was 0.042±0.011, and PPR rate was 0.051±0.016 (Table 1). No significant difference was observed between the abortion group, abortus imminens group, and control group in terms of platelet values, PDW values, MPV values, PPR values, and MPR values ($p>0.05$) (Table 2).

DISCUSSION

Platelets, which are responsible for the coagulation mechanism, have been shown to have an important role in angiogenesis

Table 1. Demographic characteristics

	Minimum-maximum	Median	Mean±SD
Age	21.0-45.0	33.0	33.0±4.9
Pregnancy week	6.0-12.0	8.1	8.1±1.6
Number of abortions	0.0-10.0	0.9	0.9±1.2
Platelet	148.0-573.0	256.7	256.7±65.6
PDW	8.5-22.2	12.2	12.2±1.8
MPV	8.0-13.1	10.2	10.2±0.8
PDW/platelet (PPR)	0.017-0.150	0.051	0.051±0.016
MPV/platelet (MPR)	0.016-0.089	0.042	0.042±0.011

MPV: Mean platelet volume, PPR: PDW/platelet count ratio, MPR: MPV/platelet count ratio, PDW: Platelet distribution width, SD: Standard deviation

and cell growth. Vascular endothelial growth factor, epidermal growth factor and basic fibroblast growth factors produced by platelets can be observed at reduced levels in women with a history of pregnancy loss. This resulting platelet hypofunction may weaken uteroplacental formation, decidual vessel formation and trophoblast development. Since all these factors may increase abortion rates, decreased platelet function during pregnancy may serve as a marker for abortion and abortus imminens¹⁰. Platelet volume indices, including MPV, PDW, and platelet count, are indicators of platelet activity and are routinely reported in complete blood count evaluations.

An increase in MPV is indicative of platelet production or increased platelet destruction. There are many studies in which MPV level is used for predictive, and diagnostic purposes. It has been observed that MPV values are increased in acute infections and septicemia cases, and the increase in thrombocytosis and megakaryocyte ploidy is shown as the cause^{11,12}. In studies conducted in the field of obstetrics, it has been found that MPV is associated with premature rupture of membranes, preeclampsia, recurrent pregnancy loss and first trimester abortion risk¹³⁻¹⁶. In a study by Mete Ural et al.¹⁷ in which they examined laboratory parameters in predicting the risk of abortion, no statistically significant difference was observed between the patients who had abortion and the patients in the control group in terms of MPV values, as in our study.

Many studies have also been conducted on the MPV/platelet ratio. It has been reported that the rate of MPR, which is a

thromboinflammatory marker, is significant in conditions such as endothelial dysfunction, thrombosis, and inflammation¹⁸. In addition, MPR has been found to be increased in patients with hepatocellular carcinoma, with accompanying cirrhosis and with increased fibrosis^{19,20}. In addition, the MPR rate was found to be significant in differentiating iron deficiency anemia from other types of anemia²¹. In our study, however, no difference was found between MPR and predicting the risk of abortion. We thought that this difference obtained in our study was due to the variability of predisposing factors.

PDW, a marker showing changes in platelet size and platelet activation, has been reported to be significant in predicting mortality in patients with sepsis and in intensive care units²²⁻²⁴. In another study conducted in newborns, it was shown that PDW levels were significantly higher in cases of late-onset neonatal sepsis²⁵. High values of PDW indicate the presence of mature and immature cells simultaneously circulating. This increase can also be considered as an indication that an abnormal thrombosis may occur²⁶.

Preoperative low PDW value is an indicator of a bad prognostic factor in gastric cancer cases, while a preoperative high PDW value is an indicator of a poor prognostic factor in melanoma and larynx cancer cases²⁷⁻²⁹. In two studies on recurrent pregnancy loss, PDW values were found to be statistically significantly increased compared to control groups^{17,30}. In another study showing the prediction of abortion risk, similar

Table 2. Evaluation of laboratory parameters

	Abortion		Abortus imminens		Control		p	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median		
Platelet	249.7±49.5	240.0	259.5±75.1	232.5	261.0±69.4	250.5	0.811	K
PDW	12.2±1.9	12.0	12.1±1.8	12.0	12.2±1.6	12.0	0.950	K
MPV	10.2±0.8	10.1	10.1±0.9	10.2	10.1±0.8	10.2	0.946	K
PDW/platelet	0.051±0.016	0.050	0.051±0.017	0.052	0.050±0.015	0.047	0.798	A
MPV/platelet	0.043±0.010	0.043	0.042±0.012	0.044	0.042±0.011	0.040	0.752	A

MPV: Mean platelet volume, PPR: PDW/platelet count ratio, MPR: MPV/platelet count ratio, PDW: Platelet distribution width, SD: Standard deviation

^AANOVA/^KKruskal-Wallis (Mann-Whitney U test)

to our study, no significant difference was found in the PDW value¹⁵.

Although a case-control study showed that high PPR rate at hospital admission was a predictor of mortality, in our study, PPR rate was not found to be significant in predicting abortion and abortion imminence. We attributed this difference to the fact that the people included in our study were included in the study before any thrombocyte process that could pose these risks started³¹.

Study Limitations

The first limitation of our study is that it is a retrospective study with few series. Second limitation can be due to the difficulty of obtaining precise results at high accuracies with a single measurement of laboratory parameters.

CONCLUSION

In conclusion, there was no significant effect of MPV and PDW values, MPV/platelet and PDW/platelet ratios in predicting the risk of abortion and abortus imminens in first trimester healthy pregnant women. Large-scale prospective studies are needed to confirm the relationship between abortion risk and laboratory parameters in pregnant women.

Ethics

Ethics Committee Approval: This study was approved by the Maltepe University Clinical Research Ethics Committee (decision number: 2020/900/48, date: 17.06.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.G., E.D.T., Concept: A.G., A.Ç., Design: A.G., A.Ç., Data Collection or Processing: A.G., E.D.T., Analysis or Interpretation: A.G., K.A., A.Ç., Literature Search: A.G., K.A., E.D.T., A.Ç., Writing: A.G., K.A., A.Ç.

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

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Role of Insulin Resistance in the Development of Atrial Fibrillation

Atriyal Fibrilasyon Gelişiminde İnsülin Direncinin Rolü

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ABSTRACT

Aim: To investigate the relationship between insulin resistance (IR) and atrial fibrillation (AF) in patients without overt diabetes.

Materials and Methods: Patients aged ≥ 18 years without chronic disease other than hypertension were included in the study. Medical histories were obtained, and detailed physical examination, blood tests and electrocardiography were performed. Patients with overt diabetes were excluded from the study. The patients were evaluated in two groups [normal sinus rhythm (NSR) and AF groups]. The presence of IR was analyzed.

Results: Two hundred patients (the mean age, 67.33 ± 8.37 years; 108 females), of whom 132 (66%) had NSR and 68 (34%) had AF, were included in the study. There was no difference between the groups regarding fasting plasma glucose levels (102.65 ± 7.49 mg/dL and 99.68 ± 9.46 mg/dL, respectively; $p=0.09$). A significant difference was found regarding fasting insulin levels (11.06 ± 2.71 mg/dL and 8.48 ± 2.64 mg/dL, respectively; $p<0.0001$). The mean IR [homeostatic model assessment (HOMA-IR)] was significantly higher in the AF group than in the NSR group (2.90 ± 0.79 and 2.10 ± 0.46 , respectively; $p<0.0001$). The proportion of patients with IR (HOMA-IR >2.4) was significantly higher in the AF group than in the NSR group (76.47% and 28.78%, respectively; $p<0.0001$). Regression analyses were performed. Multivariate regression analysis showed that each unit increase in HOMA-IR increased the risk of AF for 2.56-fold.

Conclusion: The main factor for the frequent coexistence of diabetes mellitus and AF was considered to be IR rather than hyperglycemia. Early detection and treatment of IR can reduce AF development and associated morbidity and mortality.

Keywords: Diabetes mellitus, insulin resistance, arrhythmia, atrial fibrillation

ÖZ

Amaç: Çalışmamızın amacı aşikar diyabeti olmayan hastalarda insülin direncinin (IR) atriyal fibrilasyon (AF) ile ilişkisini araştırmaktır.

Gereç ve Yöntem: Çalışmamıza 18 yaş ve üzeri hipertansiyon dışında kronik hastalığı olmayan hastalar dahil edildi. Hastaların tıbbi öyküleri alındı, fizik muayeneleri ve kan tahlilleri yapıldı ve elektrokardiogramları çekildi. Tetkiklerinde aşikar diyabet saptanan hastalar çalışma dışı bırakıldı. Hastalar normal sinüs ritminde (NSR) olan grup ve AF'si olan grup olmak üzere ikiye ayrıldı ve IR analiz edildi.

Bulgular: Çalışmaya 132'si (%66) NSR'de ve 68'i (%34) AF ritminde olan toplam 200 hasta (108 kadın, yaş ortalaması $67,33 \pm 8,37$ yıl) dahil edildi. NSR'de ve AF ritminde olan hastalar arasında açlık plazma glikoz seviyeleri açısından fark bulunmazken (sırası ile $102,65 \pm 7,49$ mg/dL ve $99,68 \pm 9,46$ mg/dL; $p=0,09$), açlık insülin düzeyi açısından anlamlı bir fark tespit edildi (sırasıyla $11,06 \pm 2,71$ mg/dL ve $8,48 \pm 2,64$ mg/dL; $p<0,0001$). İnsülin direnci [homeostatik model değerlendirmesi (homeostatic model assessment HOMA-IR)] ortalaması AF grubunda NSR grubuna göre anlamlı düzeyde yüksek tespit edildi (sırası ile $2,90 \pm 0,79$ ve $2,10 \pm 0,46$; $p<0,0001$). İnsülin direnci olan (HOMA-IR $>2,4$) hastaların oranı AF grubunda NSR grubuna göre anlamlı olarak daha yüksek bulundu (sırasıyla %76,47 ve %28,78; $p<0,0001$). Regresyon analizleri yapıldı. Çok değişkenli regresyon analizi HOMA-IR'deki her bir birimlik artışın AF riskini 2,56 kat artırdığını gösterdi.

Sonuç: Diyabet ve AF birlikteliğinin sık görülmesinde ana faktörün hiperglisemiden çok, öncesinde gelişen IR olduğu düşünülmüştür. IR'nin erken tespiti ve tedavisi, AF gelişimini ve ilişkili morbidite ve mortaliteyi azaltabilir.

Anahtar Kelimeler: Diyabet, insülin direnci, aritmi, atriyal fibrilasyon

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a worldwide prevalence of 2%¹. AF is associated with increases in the rates of ischemic stroke, cardiac failure, and mortality. Diabetes mellitus (DM) is one of the most important risk factors for AF. A meta-analysis of cohort and case-control studies has demonstrated that patients with DM have a 40% higher risk of AF, compared to patients without DM². Before overt DM occurs, insulin resistance (IR) and prediabetes stages are passed, but these stages may not be noticed because they are silent. Recent studies have suggested IR as a risk factor responsible for the development of AF³. The relationship between DM and AF has been demonstrated, but it is controversial whether the cause is hyperglycemia after overt diabetes develops or IR that develops much earlier. The aim of our study is to reveal the relationship between IR, which is a modifiable risk factor, and AF.

MATERIALS AND METHODS

Our study was approved by İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (decision number: 77, approval date: 21.01.2021) and conducted in accordance with 1975 Helsinki Declaration and its amendment in 2013. The study was conducted in the Internal Medicine Clinic of İstanbul Medipol University Medical Faculty Hospital between the dates of January 2020-June 2021. The patients were informed about the study and a consent form was signed. Patients aged 18 years and older, who had systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg after two measurements during our examination, or who were using antihypertensive medication, were included in the study. For the power analysis, the study of Lee et al.⁴ was taken as reference. Considering the prediction between the new-onset AF and high homeostatic model assessment for insulin resistance (HOMA-IR) with hazard ratio=1.61, 95%, confidence interval=1.14-2.29 and p=0.007, the sample size per group was calculated as minimum 60, with a type 1 error of 0.05 and the strength of the study being 80%. With a 20% loss, a total of

200 patients were incorporated in the study. Medical histories of the patients were taken, and detailed physical examination including weight, height and body mass index (BMI, kg/m²) was performed. Blood tests including fasting plasma glucose, fasting insulin, HOMA-IR, hemoglobin A1c, lipid profile, kidney and liver functions, thyroid functions, serum electrolytes and electrocardiograms were taken. Patients with secondary hypertension, known diabetes, and fasting blood sugar of ≥ 126 mg/dL, those using antidiabetic drugs, uncontrolled thyroid patients, those with known cardiovascular disease or heart failure, those receiving oncological treatment, those with neurological disease and those who did not want to participate in the study were excluded from the study. The patients were divided into two groups as the normal sinus rhythm (NSR) group and AF group and analyzed for the presence of IR. Patients with a HOMA-IR value >2.4 were considered IR.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS, Inc., Chicago, IL, USA). Continuous and quantitative variables were expressed as mean and standard deviation. The chi-square analysis was performed for discrete qualitative variables. Unpaired Student's t-test was used to analyze continuous variables. The correlation between the presence of AF and the presence of IR was evaluated and the Pearson's number (r value) was recorded. A correlation above 30% was considered a significant relationship. A p value of <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses including HOMA-IR, BMI, age, and gender were performed.

RESULTS

The present study included 200 patients (108 females, 92 males) with a mean age of 67.33 ± 8.37 years. The proportion of patients with NSR was 66% (n=132; 72 females, 60 males) and the proportion of patients with AF was 34% (n=68; 36 females, 32 males). The mean age was 66.41 ± 8.58 years for the patients with AF and 67.80 ± 8.29 years for those with NSR. The demographic characteristics and findings of study parameters

Table 1. Demographic characteristics and findings of study parameters in the study groups

	AF n=68	Patients with NSR n=132	p
Female/male, n/n	36/32	72/60	0.23
Mean age, years, mean $\pm$ SD	66.41 $\pm$ 8.58	67.80 $\pm$ 8.29	0.44
Fasting blood glucose level, mg/dL, mean $\pm$ SD	102.65 $\pm$ 7.49	99.68 $\pm$ 9.46	0.09
Fasting insulin level, mg/dL, mean $\pm$ SD	11.06 $\pm$ 2.71	8.48 $\pm$ 2.64	<0.0001
Patients with IR (a HOMA-IR of >2.4), n (%)	52 (76.5)	38 (28.8)	<0.0001
Mean HOMA-IR, mean $\pm$ SD	2.90 $\pm$ 0.79	2.10 $\pm$ 0.46	<0.0001
Body mass index	30.43 $\pm$ 3.89	26.18 $\pm$ 5.32	<0.0001

AF: Atrial fibrillation, NSR: Normal sinus rhythm, n/n: Number/number, SD: Standard deviation, IR: Insulin resistance, HOMA-IR: Homeostatic model assessment for insulin resistance

(age, gender, fasting plasma glucose level, fasting insulin level, BMI and HOMA-IR value) in the NSR and AF groups are presented in Table 1. No significant difference was found between the patients with NSR and AF in terms of age and sex distribution ($p=0.44$ for age and $p=0.23$ for sex). While no significant difference was found between the patients with AF and NSR in terms of fasting plasma glucose level (102.65 ± 7.49 mg/dL and 99.68 ± 9.46 mg/dL, respectively; $p=0.09$), there was a significant difference between the patients with AF and NSR in terms of fasting insulin level (11.06 ± 2.71 mg/dL and 8.48 ± 2.64 mg/dL, respectively; $p<0.0001$) and HOMA-IR value (2.90 ± 0.79 and 2.10 ± 0.46 , respectively; $p<0.0001$). IR was found in 38 (28.8%) of 132 patients with NSR and 52 (76.5%) of 68 patients with AF; the proportion of patients with IR was significantly higher in the patients with AF ($p<0.0001$). A positive significant correlation was found between AF and HOMA-IR ($r=0.43$, $p<0.0001$). The mean BMI was 30.43 ± 9.89 kg/m² for the patients with AF and 26.18 ± 5.32 kg/m² for the patients with sinus rhythm. A significant positive correlation was found between AF and BMI ($r=0.33$, $p<0.05$). Moreover, a significant positive correlation was also revealed between fasting blood glucose, fasting insulin, HOMA-IR and BMI ($r=0.39$, $p<0.0001$, $r=0.62$, $p<0.0001$ and $r=0.62$, $p<0.0001$, respectively). The effect of age, fasting blood glucose, fasting insulin level, HOMA-IR and BMI on AF were evaluated by using univariate logistic regression. Fasting blood glucose, fasting insulin level, HOMA-IR and BMI were found to be significant. HOMA-IR was calculated from fasting blood level and fasting insulin level; therefore, only HOMA-IR and BMI parameters were included in the multivariate logistic regression analysis to avoid multicollinearity. According to the multivariate logistic regression model, only HOMA-IR affects AF. Each "1" unit increase in HOMA-IR causes 2.56 times more AF (Table 2).

DISCUSSION

Patients with DM are at high risk for developing AF and AF-related morbidity and mortality⁵. It is controversial whether the reason for the frequent occurrence of AF in diabetic patients is hyperglycemia that occurs after the development of overt diabetes or IR that occurs much earlier. In recent years, studies have been conducted suggesting that the main cause is IR^{6,7}.

Accordingly, we aimed to investigate whether hyperglycemia or a much earlier IR was the predominant factor in the development of AF and therefore only patients with IR were included in this study and patients with overt DM were excluded. AF is the most common arrhythmia in the world and its incidence increases with age. Hypertension and AF are frequently seen together due to both having common risk factors and common mechanisms involved in the pathogenesis⁸. Left ventricular hypertrophy and left atrial remodeling caused by hypertension are thought to be responsible for the development of AF⁹. All of 200 patients included in our study were hypertensive and their mean age was high (67.33 ± 8.37 years), so we detected a high rate of AF (34%). In this study, when the group with AF and the group with NSR were compared, no significant difference was found between the two groups in terms of age, gender, and mean fasting blood sugar. The mean of BMI, fasting insulin and HOMA-IR were found to be significantly higher in the group with AF. When the multivariate logistic regression analysis was evaluated, it was determined that only HOMA-IR affected AF. According to the result of the analysis, every 1 unit increase in HOMA-IR value causes 2.56 times more AF. Before the appearance of overt DM, the IR phase is passed. Increased free fatty acid levels (lipotoxicity) and hyperglycemia (glucotoxicity) in the circulation due to overnutrition, sedentary life and metabolic disorders are the factors that initiate and maintain IR. A prospective study was conducted to investigate the contribution of IR to the risk of long-term incidence of AF in 8,175 subjects. Subjects without DM and AF were initially included in the study and were followed up for AF development at biennial controls. During a median follow-up of 12.3 years, 136 subjects developed AF (incidence ratio: 1.89/1,000 patient-years) and it was reported that patients with IR had a 60% higher risk of developing AF than those without⁴.

The Action to Control Cardiovascular Risk in Diabetes study found that aggressive DM management aimed at maintaining HbA1c $<6\%$ and failed to reduce the incidence of AF compared to a standard therapy targeting HbA1c 7.0-7.9%¹⁰. These studies suggest that the main factor in the development of AF is IR rather than hyperglycemia. Pathophysiologically, changes due to IR including inflammation, endothelial dysfunction, and

Table 2. Evaluation of parameters affecting AF

	Univariate logistic regression			Multivariate logistic regression		
	B	OR	p	B	OR	p
Age	-0.020	0.90 (0.95-1.02)	0.265	-	-	-
Fasting blood glucose	0.089	1.09 (1.05-1.13)	<0.001	-	-	-
Fasting insulin level	0.337	1.4 (1.24-1.58)	<0.001	-	-	-
HOMA-IR	1.111	3.04 (2.06-4.47)	<0.001	0.938	2.56 (1.59-4.12)	<0.001
BMI	0.126	1.13 (1.07-1.20)	<0.001	0.041	1.04 (0.97-1.12)	0.254

OR: Odds ratio with 95% confidence interval (lower-upper limit), BMI: Body mass index, HOMA-IR: Homeostatic model assessment for insulin resistance

myocardial steatosis lead to atrial dilatation and structural and electrical remodeling and thereby results in AF¹¹.

In a study conducted on rats to examine the relationship between IR and AF at the cellular level, it was revealed that IR was associated with various aspects of atrial remodeling, including increased oxidative stress, increased intracellular calcium, increased interstitial fibrosis, and increased risk of arrhythmia¹². After demonstrating the relationship between IR and AF development, studies focused on whether agents that break IR could reduce the incidence of AF development. In a meta-analysis, it was shown that thiazolidinones led to a 30% reduction in the risk of developing AF¹³. In a study conducted in Thailand, newly diagnosed type 2 DM patients who received metformin monotherapy were compared with those who did not receive drug therapy, and it was found that metformin reduced the rate of development of AF in diabetic patients¹⁴. These studies have shown that oral antidiabetic agents, which break IR, can prevent atrial myocyte structural remodeling by reducing intracellular oxidative stress and improving IR may be effective in preventing AF in patients with prediabetes¹⁵. In our study, no gender difference was found between patients with NSR and those with AF. A cohort study on more than 15,000 participants, followed for nearly 30 years, showed that the lifetime risk of developing AF was 30% in women and 36% in men¹⁶. The incidence of AF is lower in women, but the prevalence of AF is higher in women when men and women over 75 years of age are compared. AF rates are similar in men and women due to increased life expectancy^{17,18}. In our study, it was thought that the reason why there was no significant difference between the two groups in terms of gender was the high mean age of the participating patients. IR almost always accompanies obesity, and many studies have shown a relationship between obesity and AF¹⁹⁻²¹. In a meta-analysis including 16 studies, it was found that the risk of AF increased by 49% in individuals with a BMI above 30 kg/m²²². Another study reported that weight management provided beneficial cardiac remodeling and a reduction in AF burden and severity²³. In our study, the mean BMI value was calculated as 30.4 kg/m² in patients with IR and as 26.2 kg/m² in patients without IR. Consistent with these studies, AF was detected more frequently in patients with high BMI and IR in our study.

Study Limitations

Our study has some limitations. Firstly, it is a single-center study conducted on 200 patients. There is a need for multicenter studies with more patients on the subject. The second limitation of the study is that instant electrocardiography was taken from the patients. This may have caused us to miss patients with paroxysmal AF. Finally, the third limitation of the study is that it is a cross-sectional study. The presence of AF and IR were examined simultaneously. Therefore, although we found a

significant positive correlation between these two conditions, it is difficult to clearly reveal the causal relationship. It would be beneficial to conduct large-scale cohort studies that clearly reveal the cause and effect relationship on the subject.

CONCLUSION

Our study has shown that each unit increase in IR increases the risk of AF 2.56 times. The relationship between DM and AF is clear; however, the results of our study suggest that hyperglycemia has a minor role in this relationship contrary to what was previously suggested, and the main reason was thought to be IR developed much earlier. Early detection and treatment of modifiable risk factors such as IR responsible for the development of AF can reduce the risk of developing AF, which causes serious morbidity and mortality.

Ethics

Ethics Committee Approval: This study was approved by Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (decision number: 77, approval date: 21.01.2021).

Informed Consent: The patients were informed about the study and a consent form was signed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.E., Concept: E.Y., Design: E.Y., Data Collection or Processing: D.E., Analysis or Interpretation: E.Y., Literature Search: E.Y., Writing: E.Y., D.E.

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Trimester Specific Reference Ranges for Thyroid Hormones in Pregnancy with Multiples of Median Values

Gebelikte Tiroid Hormonlarının Medyan Değerlerin Katları ile Birlikte Trimester Spesifik Referans Aralıkları

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ABSTRACT

Aim: To establish trimester and population based laboratory-specific rational reference ranges with multiples of median (MoM) values for thyroid hormones.

Materials and Methods: The study was conducted in the obstetrics outpatient clinic of a tertiary health care center between April, 2021 and August, 2021. Healthy pregnant women without any risk factors and antithyroperoxidase positivity were recruited for all three trimesters. Serum thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free triiodo-thyronine (FT3) levels were measured by the electrochemiluminescence technique. Trimester specific reference ranges were determined with 5. and 95. percentiles of TSH, FT3 and FT4 values with MoM values.

Results: Overall, 484 healthy pregnant women, including 140 women in their first trimester, 204 women in their second trimester and 140 women in their third trimester were recruited. In the first trimester, 90% (n=126) women's TSH levels were within the reference limits (0.19-3.25 uIU/mL and 0.19-3.25 MoM) and 11.1% (n=14) had TSH levels above 2.5 uIU/L. For second trimester, 90.2% (n=184) had TSH levels within the reference limits (0.65-3.83 uIU/mL and 0.4-2.36 MoM) and 8.15% (n=15) had TSH levels over 3 uIU/L. In the third trimester, 90.7% (n=127) women's TSH levels were within reference limits (0.62-3.78 uIU/mL and 0.39-2.35 MoM) and 3.15% (n=4) had TSH levels over 3 uIU/L.

Conclusion: Accurate diagnosis and management of thyroid disease for pregnant women is crucial for maternal-fetal outcomes. Established reference ranges for three trimesters in this study were all higher than the recommended fixed ranges of 2011 American Thyroid Association guideline.

Keywords: Electrochemiluminescence, pregnancy, multiples of median, thyroid hormone, trimester

ÖZ

Amaç: Popülasyon ve laboratuvara özgü tiroid hormonları için trimester spesifik rasyonel referans aralıkları oluşturmaktır.

Gereç ve Yöntem: Çalışma üçüncü basamak bir sağlık kuruluşunda kadın doğum polikliniğinde Nisan 2021-Ağustos 2021 tarihleri arasında gerçekleştirildi. Her üç trimesterde de herhangi bir risk faktörü ve antitiroperoksidaz pozitifliği olmayan sağlıklı gebeler çalışmaya alındı. Serum tiroid stimulan hormon (TSH), serbest tiroksin (FT4) ve serbest triiyodo-tironin (FT3) düzeyleri elektrokemilüminesans tekniği ile ölçüldü. Trimester spesifik referans aralıkları, medyan değerlerin katları (MoM) ile TSH, FT3 ve FT4 değerlerinin 5. ve 95. persentilleri belirlendi.

Bulgular: Toplamda, 140'ı birinci trimesterde, 204'ü ikinci trimesterde ve 140'ı üçüncü trimesterde olmak üzere 484 sağlıklı gebe çalışmaya alındı. İlk trimester için kadınların %90'ı (n=126) referans sınırlarındaydı (0,19-3,25 uIU/mL ve 0,19-3,25 MoM) ve %11,1'inin (n=14) TSH seviyeleri 2,5 uIU/L'nin üzerindeydi. İkinci trimester için, %90,2 (n=184) referans sınırlarında (0,65-3,83 uIU/mL ve 0,4-2,36 MoM) TSH seviyelerine sahipti ve

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%8,15'i (n=15) 3 uIU/L'nin üzerinde TSH seviyelerine sahipti. Üçüncü trimesterde kadınların %90,7'si (n=127) referans sınırlarında (0,62-3,78 uIU/mL ve 0,39-2,35 MoM) ve %3,15'i (n=4) 3 uIU/L'nin üzerinde TSH değerlerine sahipti.

Sonuç: Gebe kadınlarda tiroid hastalığının doğru teşhisi ve yönetimi maternal-fetal sonuçlar için çok önemlidir. Bu çalışmada üç trimester için belirlenen referans aralıklarının tümü, 2011 Amerikan Tiroid Birliği kılavuzunun önerilen sabit aralıklarından daha yüksek bulunmuştur.

Anahtar Kelimeler: Elektrokemilüminesans, gebelik, medyan değer, tiroid hormonu, trimester

INTRODUCTION

Diagnosis and management of thyroid disorders are important for a healthy pregnancy. Thyroid dysfunction in pregnancy can lead to adverse pregnancy outcomes including miscarriage, preterm birth, low birth weight, preeclampsia, abruptio placentae, and stillbirth¹⁻³. The thyroid gland of the fetus does not function until the 10th-12th weeks of gestation and therefore, cannot produce hormones properly until the 20th week³. During these weeks, maternal thyroid hormones reach the embryo through the placenta and play a crucial role in the development of the fetus⁴. In addition, substantial new evidence supports the importance of thyroid hormone in the neurological development of the fetus⁵.

Diagnosis of thyroid dysfunction is mainly based on the measurement of thyrotrophin or thyroid-stimulating hormone (TSH) and free thyroxine (FT4)⁶. Pregnancy is associated with increased renal iodine excretion, thyroxine binding globulin, thyroid hormone synthesis, and human chorionic gonadotropins (hCG) thyroid stimulatory actions⁷. Thyroid function tests in pregnant women are affected by all of these factors⁷. The prevalence of thyroid dysfunction during pregnancy is 2-4%³ but the diagnosis is challenging due to undetermined population-based cut-off levels. The laboratory reference ranges do not indicate the relationship between thyroid hormone levels and clinical illness⁸. A reference range for TSH with an upper limit of 2.5 mU/l for the first trimester and 3.0 mU/l for the second or third trimester to diagnose subclinical and overt hypothyroidism are generally used³. With the use of fixed cut-off values for upper limits (2.5-3 mU/l), 8-28% of TSH measurements are accepted as high⁹. If population-based pregnancy-specific reference range was used for the upper limit for TSH, 3-4% of the measurements would be accepted as high and these population-based pregnancy-specific upper limits were generally found to be above 2.5 or 3 mU/l in the literature⁹. Recently, the 2017 American Thyroid Association (ATA) and the American College of Obstetricians and Gynecologists guidelines recommended calculating and using pregnancy-specific and laboratory-specific reference ranges for TSH and FT4 to diagnose thyroid dysfunction in pregnancy¹⁰.

The aim of this study was to establish trimester and population based laboratory-specific rational reference ranges with multiples of median values (MoM) for thyroid hormones.

MATERIALS AND METHODS

The study was conducted in the obstetrics outpatient clinic of a tertiary health care center between April, 2021 and August, 2021. The University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee approved the study (decision number: 2021/146 date: 21.04.2021). The study was registered to ClinicalTrials.gov Protocol Registration and Results System with NCT04860622 clinical trial number. Written consent was obtained from the participating women.

The women with a singleton pregnancy in any trimester, who applied to the outpatient clinic for routine antenatal obstetric care with iodized salt consumption or iodine supplementation, were recruited for the study.

Exclusion Criteria

- Pregnant women with *in vitro* fertilisation pregnancy, family history of thyroid disease, pre-existing thyroid disease, using thyroid interfering medication, with other autoimmune diseases and any pregnancy complications (gestational diabetes, hyperemesis, hypertension) were excluded from the study in the first evaluations.
- The pregnant women with a history of diabetes or pregnancy complications in previous pregnancies were also excluded.
- If pregnancy complications like gestational diabetes, hypertensive disorders occurred in follow-up of pregnancy before final analysis, the pregnant women recruited within the first trimester were excluded.
- The women who had anti-thyroperoxidase (anti-TPO) over 34 IU/mL and with any reported abnormality in the sonographic thyroid evaluation were excluded as the second step of exclusion from reference interval assessment.

The gestational age, gravidity, parity, and the number of abortions were all questioned in the routine obstetric care of pregnant women. The initially selected cohort of pregnant women were tested for beta-hCG, TSH, FT4, free triiodo-thyronine (FT3) and anti-TPO. In addition, women were directed to sonographic thyroid evaluation if possible. The size of the anti-TPO negative study cohort was determined according to previous recommendations in this subject about thyroid function reference intervals during pregnancy³.

Gestational age of women was determined by the last menstrual period and crown-rump-length measurement

by ultrasound scan together. When there was a significant difference between the two dates, the ultrasound scan was used to determine the gestational age. The first trimester of pregnancy was defined as between 7 weeks and 13 weeks and 6 days, the second trimester between 14 weeks and 27 weeks and 6 days, and the third trimester as ≥ 28 weeks until birth.

Serum TSH, FT4 and FT3 and anti-TPO were measured by the electrochemiluminescence (ECL) technique with Elecsys 801 analyzer using commercially available kits of Roche Diagnostics (Mannheim, Germany). Venous blood samples were collected from each recruited subject after 8–10 hours of fasting and tested for TSH, FT4, FT3 and anti-TPO. Reference ranges for adults used in the laboratory in which the assay was performed were as follows: TSH: 0.50–5.10 uIU/mL, FT4: 0.93–1.7 ng/dL, FT3: 2.04–4.4 pg/dL. The inter and intraassay variations were 1.0% and 1.5%, respectively, for TSH, 1.6% and 3.2%, respectively, for FT4 and 1.9% and 2.2%, respectively, for FT3.

Thyroid sonographic evaluation was performed by an experienced sonographer using Toshiba Aplio 300 (Toshiba Medical Systems, Tokyo, Japan) with 7.5 MHZ linear transducer. Any abnormality reported by the sonographer was taken for the exclusion of the subject from the present study.

Statistical Analysis

The collected data were analyzed using the Statistical Package for the Social Sciences software version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the demographic data was assessed using the Shapiro-Wilk test. Demographic data are summarized as the median $\pm$ interquartile range for non-normally distributed data and as the mean $\pm$ standard deviation for normally distributed data. One-way ANOVA and Kruskal-Wallis tests were used for comparing continuous variables when appropriate. Since the subjects were clinically selected as healthy, outlier exclusion was not performed. TSH, FT3 and FT4 values were log-transformed for normality assumption. Trimester specific reference ranges were determined with 5. and 95. percentiles of TSH, FT3 and FT4 values. MoM values of TSH, FT3 and FT4 values were calculated and reference ranges

of each trimester were found at 5. and 95. percentiles. A p value of <0.05 was considered to indicate a significant difference.

RESULTS

In total, 526 women were enrolled in this study. Forty women due to high anti-TPO levels and 2 women with thyroiditis findings in the sonographic evaluation were excluded. Ultrasonography/thyroid sonographic evaluation could only be applied to 50 pregnant women due to limited resources. Overall, 484 healthy pregnant women, including 140 women in the first trimester, 204 women in the second trimester and 140 women in the third trimester, were recruited for the final analysis of the study. Demographic and obstetric characteristics of women and laboratory results are summarized in Table 1 in accordance with each trimester. Reference intervals (median, 5th and 95th percentiles) for thyroid hormone levels and MoM values are presented in Tables 2, 3, and 4.

For the first trimester, TSH levels of 90% (n=126) women were within the reference ranges (0.19–3.25 uIU/mL) and 11.1% (n=14) out of 126 women had TSH levels above the fixed upper limit of the first trimester (2.5 uIU/L) (Figure 1). With regard to the second trimester, 90.2% (n=184) had TSH levels within the reference ranges (0.65–3.83 uIU/mL) and 8.15% (n=15) of 184 women had TSH levels over the fixed upper limit (3 uIU/L) (Figure 2). In the third trimester, 90.7% (n=127) of women's TSH levels were within reference ranges (0.62–3.78 uIU/mL) and 3.15% (n=4) of 127 women had TSH levels over the fixed upper limit (3 uIU/L) (Figure 3).

Within the reference ranges of first, second and third trimester TSH levels, 5 (3.97%), 7 (3.80%), and 5 (3.94%) pregnant women had FT4 level below the 5th percentile FT4 level of first, second and third trimesters, respectively.

DISCUSSION

Reference levels for the TSH, FT4 and FT3 values were determined in a healthy cohort of pregnant women for our institution. The upper reference limits were found to be above

Table 1. Demographic and obstetric characteristics and laboratory results of women in accordance with each trimester

	1 st trimester (n=140)	2 nd trimester (n=204)	3 rd trimester (n=140)	p
	Mean $\pm$ SD (min-max)	Mean $\pm$ SD (min-max)	Mean $\pm$ SD (min-max)	
Age (year)	27.9 $\pm$ 5.2 (18–46)	27.7 $\pm$ 5.6 (24–42)	28.2 $\pm$ 5.2 (19–41)	0.534
BMI (kg/m ²)	26.3 $\pm$ 8.8 (16.81–39.30)	26.8 $\pm$ 4.6 (18.21–45.49)	28.8 $\pm$ 5.0 (19.10–47.11)	0.001
	Median $\pm$ IQR (min-max)	Median $\pm$ IQR (min-max)	Median $\pm$ IQR (min-max)	
Gravidity	2 $\pm$ 2 (1–11)	2 $\pm$ 1 (1–10)	2 $\pm$ 3 (1–9)	0.501
Parity	1 $\pm$ 2 (0–8)	1 $\pm$ 2 (0–9)	1 $\pm$ 2 (0–5)	0.530
Gestational age (week)	8 $\pm$ 4.5 (7–13)	21 $\pm$ 8 (14–30)	32 $\pm$ 4 (28–39)	
	Mean $\pm$ SD (min-max)	Mean $\pm$ SD (min-max)	Mean $\pm$ SD (min-max)	
Beta-hCG (mIU/mL)	85104.1 $\pm$ 42370.0 (3689–191450)	23882.0 $\pm$ 20462.1 (1361–127444)	20139.6 $\pm$ 15733.1 (1838–77793)	N/A
TSH (uIU/mL)	1.33 $\pm$ 1 (0.02– 6.59)	1.84 $\pm$ 1 (0.01– 6.1)	1.75 $\pm$ 0.9 (0.35– 5.81)	0.000
FT4 (ng/dL)	1.2 $\pm$ 0.16 (0.75–1.65)	1.04 $\pm$ 0.14 (0.68–1.52)	0.97 $\pm$ 0.12 (0.66– 1.22)	0.000
FT3 (pg/dL)	3.29 $\pm$ 0.44 (2.1–4.93)	3.02 $\pm$ 0.37 (2.14–4.28)	2.8 $\pm$ 0.16 (0.75–1.65)	0.000

TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, BMI: Body mass index, SD: Standard deviation, Min-max: Minimum-maximum, beta-hCG: Beta-human chorionic gonadotrophin, IQR: Interquartile range

Table 2. Reference intervals (median, 5th and 95th percentiles) for TSH levels (uIU/mL) and MoM values

	5 th percentile (CI) value	5 th percentile MoM value	Median	CI value	95 th percentile MoM value
First trimester (n=140)	0.19 (0.09-0.31)	0.19	1.02	3.31 (2.75-3.60)	3.25
Second trimester (n=204)	0.65 (0.48-0.79)	0.4	1.62	3.83 (3.34-4.46)	2.36
Third trimester (n=140)	0.62 (0.50-0.73)	0.39	1.61	3.78 (2.91-4.08)	2.35

TSH: Thyroid-stimulating hormone, MoM: Multiples of median, CI: Confidence interval

Table 3. Reference intervals (median, 5th and 95th percentiles) for FT4 levels (ng/dL) and MoM values

	5 th percentile (CI) value	5 th percentile MoM value	Median	95 th percentile (CI) value	95 th percentile MoM value
First trimester (n=140)	0.97 (0.95-1)	0.82	1.19	1.51 (1.4- 1.57)	1.27
Second trimester (n=204)	0.83 (0.8-0.86)	0.81	1.03	1.29 (1.26-1.4)	1.25
Third trimester (n=140)	0.78 (0.72- 0.82)	0.81	0.96	1.17 (1.14-1.2)	1.22

FT4: Free thyroxine, MoM: Multiples of median, CI: Confidence interval

Table 4. Reference intervals (median, 5th and 95th percentiles) for FT3 levels (pg/dL) and MoM values

	5 th percentile (CI) value	5 th percentile MoM value	Median	95 th percentile (CI) value	95 th percentile MoM value
First trimester (n=140)	2.59 (2.47-2.73)	0.78	3.32	3.98 (3.86- 4.14)	1.20
Second trimester (n=204)	2.44 (2.35- 2.54)	0.81	3.01	3.61 (3.53- 3.78)	1.20
Third trimester (n=140)	2.2 (2.14- 2.35)	0.81	2.73	3.52 (3.3-3.82)	1.29

FT3: Free triiodothyronine, MoM: Multiples of median, CI: Confidence interval

the recommended-fixed upper limits of 2.5 uIU/L and 3 uIU/L at the 2011 ATA guideline. The fixed upper limits of 2.5 uIU/L and 3 uIU/L would lead to overdiagnosis and overtreatment of 11.1%, 8.15%, and 3.15% of the first, second and third trimesters, respectively, when compared with new reference values in this study.

There is a debate about universal screening for thyroid dysfunction and screening mainly recommended for pregnant women with risk^{6,11,12}; however, healthcare providers are widely performing universal screening¹³. Furthermore, there is an ongoing debate about whom to treat, when to treat, and whether treatment is useful based on currently available data¹². In this regard, locally established reference ranges for thyroid function at the population level in pregnant women without thyroid disease were recommended^{6,10}.

Several studies were carried out following the recommendations of recent guidelines about population-based reference intervals of thyroid hormones in pregnant women^{3,14-16}. To the best of our knowledge, there were only two studies that emerged from our country^{14,15} at the time of writing this paper. In these studies, 2.5 and 97.5 percentiles were taken as reference intervals. In the study of Akarsu et al.¹⁴, reference intervals of 0.49-2.33 mIU/L, 0.51-3.44 mIU/L, and 0.58-4.31 mIU/L for TSH were found for the first, second and third trimesters, respectively. The first trimester upper reference limit was lower than the fixed upper limit of the 2011 ATA guideline and lower than the upper limit found in the present study. Bulur et. al.¹⁵ found their reference intervals for TSH as 0.005-3.65 mIU/L for the

first, 0.011-3.63 mIU/L for the second and 0.2-3.46 mIU/L for the third trimesters. The upper limits in that study were higher than the fixed 2011 ATA guideline upper limits and our upper reference limits. Regarding FT4 limits, the limits were lower in this study compared to the present study and the limits were declining from the first to the third trimester, similar to our study.

In the present study, ECL kits were used for the measurement of thyroid hormone levels. The other studies using ECL kits proposed higher reference limits for TSH than the fixed ATA limits of 2011¹⁷⁻¹⁹. In the studies of Marwaha et al.¹⁸ and Kurioka et al.¹⁹, the TSH mean values were found to be increasing from the first through the third trimester, and FT4 and values were declining with advancing pregnancy. These findings were similar to our study findings. However, another study of Kumar et al.¹⁷ revealed that FT4 and FT3 values were increasing from first to the second trimester and declining from second to third trimester. In our opinion, in pregnant women, TSH was first suppressed and then increased pertinently with changes in FT4, FT3, and beta-hCG levels as mentioned in a study from China²⁰.

The recent ATA guideline makes an exception for anti-TPO positive women and suggests that treatment can be considered if the TSH level is above 2.5 mU/L. Another study investigated this subject and reported that treatment for TSH levels above 4 mU/L in anti-TPO positive women was beneficial in reducing the rate of preterm delivery²¹. This beneficial effect has also existed for the anti-TPO negative women²². However, the data about the treatment of euthyroid women or subclinical hypothyroid

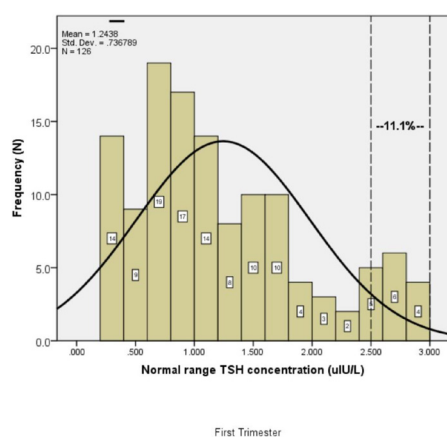


Figure 1. Distribution of serum TSH values within the normal percentile interval (5th-95th percentiles) in the first trimester

TSH: Thyroid-stimulating hormone

women with thyroid autoimmunity were limited and future randomized controlled studies with large sample sizes were needed². In the present study, adjunct to the exclusion of known thyroid disease, anti-TPO negative pregnant women were recruited for the purpose of constituting a qualified reference population.

Overt hyperthyroidism is a rare condition that affects 0.1 to 0.4% of all pregnancies²³. A suppressed (0.1 mU/L) or undetectable (0.01 mU/L) serum TSH value, as well as a FT4 and/or FT3 (or total T4 and/or total T3) measurement that exceeds the normal range for pregnancy, should be used to diagnose overt hyperthyroidism during pregnancy¹⁰. For the second and third trimesters, the recommended lower limits for TSH are 0.2 and 0.3 mU/L¹⁰. In the present study, the lower limits for TSH were above the recommended lower limits; however, it was similar to the other study from Turkey¹⁴. The TSH and FT4 values were expressed as MoM in this study, this was suggested for interpreting and comparing these values obtained by different assays^{3,8}. In a previous study that summarized the reference intervals as MoM values of TSH and FT4 during early pregnancy, the TSH MoM values changed between 0.04-0.44 for the lower limit and 2.34-3.37 MoM for the upper limit, and regarding FT4 MoM values changed between 0.71-0.80 MoM for the lower limit and 1.25-1.60 for the upper limit³. The MoM values for TSH and FT4 were within these limits in this study.

Study Limitations

The urinary iodine concentration could not be measured in the present study. The median urinary iodine concentration of the population has been used for iodine sufficiency or deficiency status of reference population²⁴. The pregnant women's iodine requirements increase with the increase in renal iodine clearance and with an increase in maternal

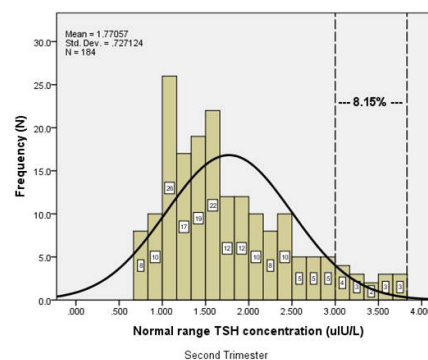


Figure 2. Distribution of serum TSH values within the normal percentile interval (5th-95th percentiles) in the second trimester

TSH: Thyroid-stimulating hormone

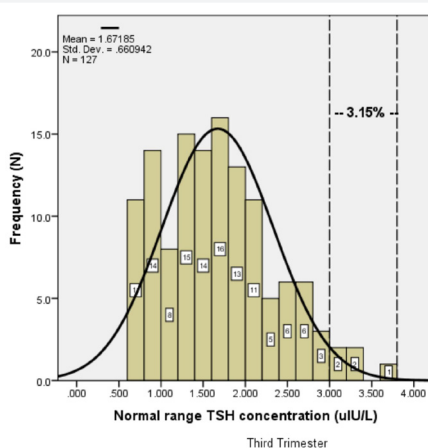


Figure 3. Distribution of serum TSH values within the normal percentile interval (5th-95th percentiles) in the third trimester

TSH: Thyroid-stimulating hormone

thyroxine production for being sufficient to mother and fetus particularly at the beginning of pregnancy^{3,24}. The urinary iodine concentration was not considered in the studies of Sun and Xia²⁵, Donovan et al.²⁶, Akarsu et al.¹⁴, and Bulur et al.¹⁵ and in a study of Kostecka-Matyja et al.²⁷, pregnant women taking iodine prophylaxis were recruited as a study cohort. In the study of Azizi et al.²⁸, the urinary iodine level measurement and thyroid ultrasonography evaluation were considered. In the present study, the pregnant women consuming iodized salt and iodine supplementation were recruited for minimizing the possible effect of iodine deficiency.

The other limitations of the current study are that the small number of patients were evaluated with thyroid ultrasonography due to limited facility and technical difficulties, and that the

present study did not last enough to be able to investigate all the maternal and neonatal outcomes of the study population.

CONCLUSION

Accurate diagnosis and management of thyroid disease for pregnant women is crucial for maternal-fetal outcomes. In the current study, trimester and laboratory-specific rational reference ranges for thyroid hormone levels with MoM values for diagnosing thyroid dysfunction were established. Established reference ranges for three trimesters were all higher than the recommended fixed ranges of the 2011 ATA guideline. Well-designed studies including maternal-fetal outcomes should be conducted to create population-based laboratory specific reference limits for pregnant women.

Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee approved the study (decision number:2021/146 date: 21.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B.T., M.Y., G.T., D.E., D.B., B.D.T., Concept: A.B.T., M.Y., B.D.T., M.A.S., N.T., Design: A.B.T., M.Y., G.T., D.E., B.D.T., M.A.S., N.T., Data Collection or Processing: A.B.T., M.Y., G.T., D.E., D.B., B.D.T., Analysis or Interpretation: A.B.T., M.Y., D.E., D.B., N.T. Literature Search: A.B.T., M.Y., D.E., D.B., M.A.S., Writing: A.B.T., M.Y., M.A.S., N.T.

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Factors Associated with Nutritional Status in Geriatric Outpatients

Ayaktan Başvuran Geriatrik Hastalarda Beslenme Durumu ile İlişkili Faktörler

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ABSTRACT

Aim: Malnutrition is a geriatric syndrome that should not be ignored considering its negative consequences in older adults. There are many factors that affect nutritional status. We aimed to determine the factors related to malnutrition in the elderly in this study.

Materials and Methods: This cross-sectional study included 356 elderly outpatients admitted to a geriatric outpatient clinic. Comprehensive geriatric assessments were performed and factors related to nutritional status were assessed. The Mini Nutritional Assessment Tool (MNA) and the Global Leadership Initiative on Malnutrition (GLIM) criteria were used to screen and diagnose malnutrition.

Results: The participants had a mean age of 72.2±6.5 years. Of the participants, 93 (26.1%) were considered malnourished according to the GLIM criteria. Malnourished participants had poorer quality of life, physical functioning, sleep quality, and higher depressive and anxiety symptoms. MNA scores were positively correlated with quality of life scores ($r=0.355$, $p=0.000$) and negatively correlated with depressive and anxiety symptoms scores ($r=-0.346$, $p=0.000$, and $r=-0.301$, $p=0.000$, respectively). Age and higher depressive symptom scores were found to be independent variables for malnutrition [$p=0.026$, Odds ratio (OR): 1.07 and $p=0.045$, OR: 1.07, respectively].

Conclusion: This study has shown that malnourished older adults are more likely to have impaired functional status, depressive and anxiety symptoms, poorer quality of life and sleep quality. Depressive symptoms and age have been found to increase the risk of malnutrition. Comprehensive geriatric assessment should be performed in all older adults to avoid undesirable consequences.

Keywords: Malnutrition, elderly, depression, quality of life, physical functioning

ÖZ

Amaç: Malnütrisyon, yaşlı erişkinlerde olumsuz sonuçları göz önüne alındığında göz ardı edilmemesi gereken bir geriatric sendromdur. Beslenme durumunu etkileyen birçok faktör vardır. Bu çalışmada yaşlılarda malnütrisyon ile ilişkili faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Bu kesitsel çalışmaya bir geriatri polikliniğine başvuran 356 yaşlı ayaktan hasta alındı. Katılımcılara kapsamlı geriatric değerlendirme yapıldı ve beslenme durumu ile ilgili faktörler değerlendirildi. Malnütrisyon tarama ve tanısı için Mini Nutritional Assessment Tool (MNA) ve Global Leadership Initiative on Malnutrition (GLIM) kriterleri kullanıldı.

Bulgular: Katılımcıların ortalama yaşı 72,2±6,5 yıl idi. Katılımcıların 93'ü (%26,1) GLIM kriterlerine göre malnütre olarak kabul edildi. Malnütrisyonu olan katılımcılar daha düşük yaşam kalitesi, fiziksel işlevsellik, uyku kalitesi ve daha yüksek depresif ve anksiyete semptomlarına sahipti. MNA puanları ile yaşam kalitesi puanları arasında pozitif ($r=0,355$, $p=0,000$), depresif ve anksiyete belirtileri puanları arasında negatif korelasyon (sırasıyla $r=-0,346$, $p=0,000$ ve $r=-0,301$, $p=0,000$) saptandı. Yaş ve yüksek depresif belirti puanları malnütrisyon için bağımsız değişkenler olarak bulundu [sırasıyla $p=0,026$, Odds oranı (OR): 1,07 ve $p=0,045$, OR: 1,07].

Sonuç: Bu çalışma, malnütrisyonlu yaşlı erişkinlerde işlevsel durumda bozulma, depresif ve anksiyete belirtileri, daha düşük yaşam kalitesi ve uyku kalitesine sahip olma olasılığının daha yüksek olduğunu göstermiştir. Depresif belirtiler ve yaşın malnütrisyon riskini artırdığı bulunmuştur. İstenmeyen sonuçlardan kaçınmak için tüm yaşlı erişkinlerde kapsamlı geriatric değerlendirme yapılmalıdır.

Anahtar Kelimeler: Malnütrisyon, yaşlı, depresyon, yaşam kalitesi, fiziksel işlevsellik

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INTRODUCTION

Malnutrition is a common geriatric syndrome with an estimated risk of 8.5% in community settings and 28% in hospital settings. Malnutrition can result in poor prognosis and increased health care costs¹. The origin of malnutrition is complex and there are many factors that reduce dietary intake in older adults (e.g., physiological decrease in appetite, physical and cognitive impairment, chewing and swallowing problems, depression, polypharmacy)². Malnutrition has poor outcomes and is associated with functional and cognitive impairment, poor wound healing, immune dysfunction, longer hospital stays, higher readmission rates, poorer quality of life, and ultimately higher mortality^{3,4}.

Depression, one of the most important public health problems, has been reported to have a prevalence of up to 38% in older adults before the COVID-19 pandemic⁵. Depression is the leading cause of weight loss in older adults due to loss of appetite and anorexia it causes^{6,7}. Many studies have shown that malnutrition is associated with depression and multiple comorbidities^{8,9}. Kaburagi et al.¹⁰ showed that handgrip strength, gait speed, and depressive symptoms scores were the predictors of malnutrition. It is not clear whether depression is the cause or the result of malnutrition, but a vicious cycle is pointed out between the two items¹¹.

Studies have shown that malnutrition is closely associated with dependency in activities of daily living and poorer quality of life^{12,13}. Additionally, Feldblum et al.¹⁴ found a significant association between geriatric syndromes, including impairments in cognitive and physical functions, malnutrition, and depressive symptoms.

Studies investigating malnutrition and related factors by performing a comprehensive geriatric assessment will also help to solve different problems in geriatric patients in the future. Therefore, in this study, we aimed to examine the relationship between nutritional status and other geriatric conditions.

MATERIALS AND METHODS

A total of 356 individuals aged ≥ 65 years, who were admitted to the Geriatric Outpatient clinic of Gaziantep University Şahinbey Research and Practice Hospital between May 2019 and May 2021, were included in this cross-sectional study. Individuals who agreed to participate in the study and did not have exclusion criteria were included. Exclusion criteria included the presence of acute or chronic inflammatory diseases, cancer, neuromuscular diseases, and additional comorbidities (severe visual and hearing impairments, osteoarthritis, peripheral arterial disease) affecting the comprehensive geriatric assessment. Other comorbid diseases including diabetes mellitus, hypertension, hyperlipidemia, coronary

artery disease, cerebrovascular diseases, neurodegenerative diseases, asthma, chronic obstructive pulmonary disease, rheumatic diseases, thyroid diseases were questioned and the most common diseases were given as sociodemographic data. The minimum sample size calculated with Epi Info software was 183 participants. Informed consent was obtained from the participants. All participants underwent a comprehensive assessment by an experienced physician, including nutritional status, activities of daily living, anxiety symptoms, depressive symptoms, mental status, sarcopenia, quality of life, and sleep quality.

Assessment of Nutritional Status

The Mini Nutritional Assessment Tool (MNA) was used to screen the nutritional status of participants. According to the tool, the scores of 24 and above are considered adequate nutritional status, the scores of 17-23.5 are considered malnutrition risk, and the scores of 17 and below are considered malnutrition¹⁵. Afterward, the Global Leadership Initiative on Malnutrition (GLIM) criteria, including 5 criteria (3 phenotypic and 2 etiologic), were used to diagnose malnutrition. Phenotypic criteria include loss of weight ($>5\%$ in the last 6 months or $>10\%$ in more than 6 months), reduced muscle mass, and low body mass index (<20 for under 70 years, <22 for under 72 years of age). Etiologic criteria include inflammation and reduced food intake. At least 1 phenotypic criterion and 1 etiologic criterion are required for the diagnosis of malnutrition. The severity of malnutrition is based on phenotypic criteria and is classified as stage 1 (moderate) and stage 2 (severe) malnutrition¹⁶. Participants were grouped as "malnourished" and "with normal nutritional status" based on GLIM criteria.

Assessment of Activities of Daily Living

The dependence in activities such as transferring, continence, bathing, toileting, dressing, and feeding was assessed with the Katz Index of Activities of Daily Living (ADL). According to the index, the total score ranges from 0 to 6, with higher scores indicating greater independence¹⁷.

Assessment of Instrumental Activities of Daily Living

The Lawton & Brody Index of Instrumental Activities of Daily Living (IADL) measures independence in housekeeping, doing laundry, using the telephone, using transportation, food preparation, shopping, managing money, and taking medicine. According to the index, the total score ranges from 0 to 8, with higher scores indicating greater independence¹⁸.

Assessment of Depressive Symptoms

The Geriatric Depression Scale (GDS), consisting of 30 questions, was used to evaluate depressive symptoms. A total score of ≥ 14 is considered depression according to the scale^{19,20}.

Assessment of Anxiety Symptoms

The Beck Anxiety Inventory (BAI), consisting of 21 questions, was used. According to the inventory, the scores of 0-7 are considered as no or minimum anxiety, 8-15 as mild anxiety, 16-25 as moderate anxiety, and 26-63 as severe anxiety²¹.

Assessment of Cognitive Functions

The Mini-Mental State Examination Test (MMSE) was used to assess the cognitive functions. The reliability and validity of the test in the Turkish population were established and the cut-off point was found as 23/24 for the diagnosis of mild dementia²².

Assessment of Quality of Life

Individuals' quality of life was assessed with the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. In the questionnaire, individuals are asked to evaluate their own health status and the index score is calculated. A score of 0 indicates death, 1 indicates perfect health, and negative values indicate someone is bedridden, dependent, and unconscious. The second part of the questionnaire, the EQ-5D visual analogue scale, asks individuals to rate their health status between 0 and 100 points²³.

Assessment of Sarcopenia

The European Working Group on Sarcopenia in Older People criteria were used to diagnose sarcopenia. Low muscle strength and mass are required according to the criteria. Handgrip strength was measured using a hydraulic hand dynamometer. A bioelectrical impedance analyzer was used to measure muscle mass. Cut-off values for handgrip strength and muscle mass were used^{24,25}.

Assessment of Sleep Quality

The Pittsburgh Sleep Quality scale (PSQI) was used. The scale has 7 components and each component is rated between 0 and 3 points. A total score of 5 and above indicates poor sleep quality²⁶. Concomitant use of five or more drugs was considered polypharmacy.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) for Windows version 22.0 (IBM SPSS Statistics, Armonk, NY) was used. The distribution of normality was checked. The Mann-Whitney U test and independent samples t-test were used to compare two independent groups. The chi-squared test was employed to evaluate the relationship between categorical variables and the Spearman's rank correlation coefficients to evaluate the relationship between numerical variables. Correlation coefficient values between 0 and 0.3 (0 and -0.3) were accepted

as weak relationship, between 0.3 and 0.7 (-0.3 and -0.7) as moderate relationship, and between 0.7 and 1.0 (-0.7 and -1.0) as strong relationship²⁷. Multivariate binary logistic regression analysis was performed by adding categorical and continuous variables to the analysis and using the "enter model" to identify independent factors of malnutrition. $p \leq 0.05$ was considered statistically significant, and additionally, p values of " ≤ 0.01 " were specified in the correlation analysis.

RESULTS

The mean age of the 356 individuals was 72.2 ± 6.5 years and 59.0% were female. Ninety-three (26.1%) participants were considered malnourished according to the GLIM criteria (85 cases stage 1 and 8 cases stage 2). The frequency of female participants and the mean age of the participants in the malnourished group were higher than those with normal nutritional status. Of the 93 malnourished patients, 4 were considered to have adequate nutritional status according to the MNA. While the ADL, IADL, MMSE and EQ-5D scores were lower in the malnourished group, the GDS, BAI and PSQI scores were higher. There was no statistically significant difference between the groups in terms of number of medications, number of comorbidities, frequency of sarcopenia and polypharmacy (Table 1).

The MNA score had a negative moderate correlation with BAI ($r = -0.301$, $p = 0.000$) and GDS ($r = -0.346$, $p = 0.000$) scores and a positive moderate correlation with EQ-5D score ($r = 0.355$, $p = 0.000$) (Table 2, 3).

Variance inflation factor (VIF) was calculated and ADL, IADL, and EQ-5D scores and number of medications were excluded due to potential collinearity problem. Multivariate logistic regression analysis was performed, and age and GDS score were found as independent variables for malnutrition ($p = 0.026$, OR: 1.07 and $p = 0.045$, OR: 1.07, respectively) (Table 4).

DISCUSSION

Our study revealed that more than a quarter of elderly outpatients were malnourished according to the GLIM criteria, and malnutrition was associated with higher depressive symptoms and poorer physical functioning, quality of life, and sleep quality. It was found that the risk of malnutrition increased as the depressive symptom scores increased.

Previous studies have shown a strong association between depression and malnutrition, similar to our results^{8,28}. A recent study has shown that malnourished older adults are 31% more likely to present depressive symptoms than those with normal nutritional status²⁹. Although the cause and effect relationship between depression and malnutrition has not been clearly clarified, depression has a significant effect on appetite and dietary intake. Low serotonin levels and altered dopamine

Table 1. Participants' socio-demographic characteristics and comprehensive geriatric assessment results (n=356)				
Variables	Normal nutritional status (n=263)	Malnourished (n=93)	p	Total (n=356)
Gender				
Female	147 (55.9%)	63 (67.7%)	0.046*	210 (59.0%)
Male	116 (44.1%)	30 (32.3%)		146 (41.0%)
Age[†]	71.7±5.8	73.9±7.8	0.004*	72.2±6.5
Number of comorbidities[#]	2 (0-7)	3 (0-8)	0.134	2 (0-8)
Number of medications[#]	4 (0-18)	5 (0-15)	0.086	4 (0-18)
Comorbidities				
Hypertension	156 (59.3%)	57 (61.3%)	0.738	213 (59.8%)
Diabetes mellitus	129 (49.0%)	47 (50.5%)	0.805	176 (49.4%)
Coronary artery disease	64 (24.3%)	29 (31.2%)	0.196	93 (26.1%)
Neurodegenerative diseases	45 (17.1%)	21 (22.6%)	0.243	66 (18.5%)
Asthma/COPD	33 (12.5%)	17 (18.3%)	0.171	50 (14.0%)
Polypharmacy	114 (43.3%)	51 (54.8%)	0.056	165 (46.3%)
Sarcopenia	94 (37.9%)	32 (37.6%)	0.966	126 (37.8%)
MNA[†]	24.4±5.1	15.7±4.3	<0.001*	22.2±6.2
Adequate nutritional status	189 (71.9%)	4 (4.3%)	<0.001*	193 (54.2%)
Risk of malnutrition	33 (12.5%)	52 (55.9%)		85 (23.9%)
Malnutrition	41 (15.6%)	37 (39.8%)		78 (21.9%)
ADL[†]	4.6±1.5	4.0±1.8	0.001*	4.5±1.6
IADL[†]	6.0±2.3	5.0±2.6	0.001*	5.7±2.4
GDS[#]	7 (0-30)	12 (0-30)	0.002*	8 (0-30)
BAI[#]	8 (0-48)	15 (0-42)	0.003*	10 (0-48)
MMSE[†]	24.1±5.3	22.1±6.2	0.004*	23.6±5.6
EQ-5D index[#]	0.58 (-0.53-1.00)	0.32 (-0.32-1.00)	0.005*	0.52 (-0.53-1.00)
EQ-5D VAS[#]	70 (20-100)	50 (10-90)	0.001*	60 (10-100)
PSQI[#]	5 (0-17)	6 (0-17)	0.042*	6 (0-17)

*p<0.05; †Data are presented as mean±SD, #Data are presented as median (minimum-maximum).
COPD: Chronic obstructive pulmonary disease, MNA: The Mini Nutritional Assessment Tool, ADL: Katz Index of Activities of daily living, IADL: Lawton & Brody index of Instrumental Activities of Daily Living, GDS: The Geriatric Depression Scale, BAI: The Beck Anxiety Inventory, MMSE: Mini Mental State Examination, EQ-5D: The European Quality of Life-5 Dimensions questionnaire, PSQI: The Pittsburgh Sleep Quality Index

release play a role in the development of depression and can also reduce appetite³⁰.

Another significant finding of our study was that age was an independent risk factor for malnutrition. A meta-analysis reported that older age and functional limitations were the determinants of malnutrition in community-dwelling older adults³¹. Chen et al.³² showed that age, comorbidities, and depressive symptoms were significantly correlated with nutritional status among frail older adults. Older adults are at higher risk of malnutrition, as aging is a risk factor for the development of chronic diseases.

In this study, ADL, IADL, MMSE and EQ-5D scores were lower in the malnourished group. Thus, malnourished older adults are more likely to suffer from physical impairment, frailty, lower cognitive function, and poorer quality of life. The relationship between nutritional scores and daily living activities scores

in our study highlights the importance of malnutrition in functionality. In a cross-sectional study involving older adults, it was found that malnutrition was strongly associated with physical dependency³³. Additionally, a recent study has shown that lower MNA scores are associated with depression and dependency in ADL³⁴.

We found a moderate positive correlation between EQ-5D and MNA scores, which is consistent with the results of Jiménez-Redondo et al.³⁵. De Oliveira et al.³⁶ showed that higher health-related quality of life scores were associated with better physical state and nutritional status in older adults³⁶. Furthermore, previous studies investigating the association between nutritional status and quality of life have suggested that good nutritional status is a protective factor for the quality of life^{37,38}. Therefore, it is important to identify malnutrition as it is associated with adverse outcomes in older adults, such

Table 2. Correlation analysis results between the variables

		MNA	Age	Number of diseases	Number of medications	ADL	IADL	EQ5D index score
MNA	r		-0.107	-0.253	-0.249	0.027	0.184	0.355
	p		0.044*	0.000**	0.000**	0.611	0.000**	0.000**
Age	r	-0.107		0.075	0.044	-0.089	-0.298	-0.297
	p	0.044*		0.159	0.403	0.092	0.000**	0.000**
Number of diseases	r	-0.253	0.075		0.624	0.093	-0.160	-0.357
	p	0.000**	0.159		0.000**	0.081	0.002**	0.000**
Number of medications	r	-0.249	0.044	0.624		0.030	-0.141	-0.271
	p	0.000**	0.403	0.000**		0.575	0.008**	0.000**
ADL	r	0.027	-0.089	0.093	0.030		0.537	0.541
	p	0.611	0.092	0.081	0.575		0.000**	0.000**
IADL	r	0.184	-0.298	-0.160	-0.141	0.537		0.666
	p	0.000**	0.000**	0.002**	0.008**	0.000**		0.000**
EQ5D index	r	0.355	-0.297	-0.357	-0.271	0.541	0.666	
	p	0.000**	0.000**	0.000**	0.000**	0.000**	0.000**	

r: Spearman rank correlation coefficient; *Significant at 0.05 level; **Significant at 0.01 level.

MNA: The Mini Nutritional Assessment Tool, ADL: Katz Index of Activities of daily living, IADL: Lawton & Brody index of Instrumental Activities of Daily Living, EQ-5D: The European Quality of Life-5 Dimensions questionnaire

Table 3. Correlation analysis results between the variables

		MNA	BAI	GDS	MMSE	HGS	PSQI
MNA	r		-0.301	-0.346	0.132	0.228	-0.277
	p		0.000**	0.000**	0.013*	0.000**	0.000**
BAI	r	-0.301		0.641	-0.105	-0.281	0.450
	p	0.000**		0.000**	0.104	0.000**	0.000**
GDS	r	-0.346	0.641		-0.331	-0.367	0.426
	p	0.000**	0.000**		0.000**	0.000**	0.000**
MMSE	r	0.132	-0.105	-0.331		0.320	-0.082
	p	0.013*	0.104	0.000**		0.000**	0.212
HGS	r	0.228	-0.281	-0.367	0.320		-0.164
	p	0.000**	0.000**	0.000**	0.000**		0.013*
PSQI	r	-0.277	0.450	0.426	-0.082	-0.164	
	p	0.000**	0.000**	0.000**	0.212	0.013*	

r: Spearman rank correlation coefficient; *Significant at 0.05 level; **Significant at 0.01 level.

MNA: The Mini Nutritional Assessment Tool, BAI: The Beck Anxiety Inventory, GDS: The Geriatric Depression Scale, MMSE: Mini Mental State Examination, HGS: Handgrip strength (kg), PSQI: The Pittsburgh Sleep Quality Index

as poor quality of life, impaired functional status, increased healthcare costs, and mortality rates³⁹.

In our study, it was also found that malnourished individuals had poorer sleep quality. A recent study has shown that poor sleep quality is significantly associated with the risk of malnutrition among older adults⁴⁰. Considering the role of sleep quality in healthy aging, the importance of adequate nutrition increases even more.

Study Limitations

Our study has several limitations. First, due to its cross-sectional nature, no cause-effect relationships between the assessment results can be suggested. Second, study participants were elderly individuals admitted to a tertiary referral hospital, and these results cannot be generalized to community-dwelling older adults. The strengths of our study are that it included an acceptable number of participants for data extraction, that there was homogeneity between the groups so that the factors

Table 4. Multivariate logistic regression analysis results of the independent variables for malnutrition

Variable	Malnutrition	
	OR (95% CI)	p value
Age	1.07 (1.01-1.13)	0.026*
Gender (female vs. male)	1.04 (0.52-2.08)	0.923
Number of diseases	1.19 (0.96-1.48)	0.108
GDS	1.07 (1.00-1.14)	0.045*
BAI	1.04 (1.00-1.08)	0.078
MMSE	0.97 (0.91-1.03)	0.386
PSQI	1.02 (0.93-1.11)	0.750
Sarcopenia	1.04 (0.98-1.09)	0.212

*p<0.05 according to multivariate binary logistic regression analysis.
CI: Confidence interval, OR: Odds ratio, GDS: The Geriatric Depression Scale, BAI: The Beck Anxiety Inventory, MMSE: Mini Mental State Examination, PSQI: The Pittsburgh Sleep Quality Index

affecting malnutrition could be clearly evaluated, and that we performed comprehensive geriatric assessments using valid tools.

CONCLUSION

In this study, age and depressive symptoms were found to be independent variables for malnutrition. We also showed that malnourished older adults were more likely to suffer from impaired functional status, depressive and anxiety symptoms, poorer quality of life and sleep quality. Our results highlight the importance of adequate nutrition and psychological support in older adults to avoid potential adverse outcomes.

Ethics

Ethics Committee Approval: This study was approved by the Gaziantep University Clinical Research Ethics Committee (decision number: 2015/296, date: 02.11.2015).

Informed Consent: Informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç., Concept: Z.A.Ö., Design: E.M.E., Z.A.Ö., Data Collection or Processing: A.Ç., Analysis or Interpretation: A.Ç., Literature Search: E.M.E., Writing: A.Ç.

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Identification of Bacterial Vaginal Microbiota via Metagenomic Approach

Bakteriyel Vajinal Mikrobiyotanın Metagenomik Yaklaşımla Tanımlanması

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ABSTRACT

Aim: The aim of the current study was to identify vaginal bacterial microbiota of 38 Turkish women using the high-throughput next-generation sequencing and metagenomic approach at different taxonomic levels from the kingdom to the species level.

Materials and Methods: Vaginal swab samples (n=38) were collected in the DNA/RNA shield collection tubes at Yeditepe University Hospital, Department of Obstetrics and Gynecology in June 2021 and DNA extraction was performed by ZymoBIOMICS DNA miniprep kit. The information related to age, marital status, preliminary diagnosis and anamnesis status of patients were collected. To determine the vaginal microbiota, a metagenomic approach was applied using 16S rRNA amplicon sequencing.

Results: The dominant phylum Firmicutes was followed by Proteobacteria, Actinobacteria, Tenericutes, Fusobacteria, and Synergistetes in the vaginal samples. *Lactobacillus* was the most abundant genus followed by *Prevotella*, *Enterobacter*, *Gardnerella*, and *Dialister*. *Lactobacillus iners* was dominant at the species level in vaginal swab samples, followed by *Gardnerella vaginalis*, *Enterobacter tabaci*, *Prevotella timonensis*, *Prevotella bivia*, and *Lactobacillus jensenii*. Canonical correspondence analysis (CCA) showed that Proteobacteria and Fusobacteria were mainly related to married/single variable with the highest percentages, whereas Actinobacteria and Tenericutes were related to age variable at the phylum level. *Campylobacter*, *Atopobium*, *Enterobacter*, and *Lactococcus* were mainly found in married/single variable with the highest percentages, whereas *Anaerococcus*, *Streptococcus*, *Sutterella*, and *Veillonella* were related to age. Moreover, CCA showed that *Campylobacter ureolyticus*, *Lb. jensenii*, and *Atopobium vaginae* were associated with married/single variable, whereas *Lactobacillus johnsonii* and *G. vaginalis* were found in age variable with the highest percentages at the species level.

Conclusion: Vaginal diseases are still a major public health concern. The vaginal microbiota, which has been studied in more depth in recent years, has been discovered to be more complicated than previously imagined thanks to technological developments. More patient investigations are needed to confirm and develop these findings.

Keywords: Metagenomics, microbiota, next-generation sequencing, vaginal tract

ÖZ

Amaç: Bu çalışmanın amacı, alem düzeyinden tür düzeyine kadar farklı taksonomik seviyelerde yüksek verimli yeni nesil dizileme ve metagenomik yaklaşım kullanarak 38 Türk kadınının vajinal bakteriyel mikrobiyotasını belirlemektir.

Gereç ve Yöntem: Yeditepe Üniversitesi Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde Haziran 2021'de DNA/RNA koruma toplama tüplerine vajinal sürüntü örnekleri (n=38) alındı ve ZymoBIOMICS DNA miniprep kiti ile DNA ekstraksiyonu yapıldı. Hastaların yaşı, medeni durumu, ön tanı ve anamnez durumu ile ilgili bilgiler toplandı. Vajinal mikrobiyotayı belirlemek için 16S rRNA amplicon DNA dizilimi kullanılarak metagenomik bir yaklaşım uygulandı.

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Bulgular: Vajinal örneklerde baskın filum Firmicutes'i Proteobacteria, Actinobacteria, Tenericutes, Fusobacteria ve Synergistetes izledi. *Lactobacillus* en fazla bulunan cins düzeyinde bakteri olup onu *Prevotella*, *Enterobacter*, *Gardnerella* ve *Dialister* izledi. Vajinal sürüntü örneklerinde tür düzeyinde *Lactobacillus iners* baskın bulundu, bunu *Gardnerella vaginalis*, *Enterobacter tabaci*, *Prevotella timonensis*, *Prevotella bivia* ve *Lactobacillus jensenii* izledi. Kanonik uyum analizi (CCA), filum düzeyinde Proteobacteria ve Fusobacteria'nın en yüksek yüzdelere evli/bekar değişkeni ile ilişkili olduğunu, ancak Actinobacteria ve Tenericutes'in yaş değişkeni ile ilişkili olduğunu gösterdi. *Campylobacter*, *Atopobium*, *Enterobacter* ve *Lactococcus* en yüksek yüzdelere evli/bekar değişkeni ile ilişkili bulunurken, *Anaerococcus*, *Streptococcus*, *Sutterella* ve *Veillonella* en yüksek yüzdelere yaşla ilişkili bulundu. Ayrıca, CCA, *Campylobacter ureolyticus*, *Lb. jensenii* ve *Atopobium vaginae* türlerinin evli/bekar değişkeni ile en yüksek yüzdelere ilişkilendirirken, *Lactobacillus johnsonii* ve *G. vaginalis* en yüksek yüzdelere yaş değişkeninde ilişkili bulundu.

Sonuç: Vajinal hastalıklar hala önemli bir halk sağlığı sorunudur. Son yıllarda teknolojik gelişmeler sayesinde daha derinlemesine çalışılan vajinal mikrobiyotanın sanıldığından daha karmaşık olduğu keşfedilmiştir. Bu bulguları doğrulamak ve geliştirmek için daha fazla hasta araştırmasına ihtiyaç vardır.

Anahtar Kelimeler: Metagenomik, mikrobiyota, yeni nesil dizileme, vajinal sistem

INTRODUCTION

Human lifestyle shifts do not only impact the health of the biosphere but likely affect our health as a result of changes in our microbial ecology. In the microscopic world, it is well known that humans are ecological harbors. The female genital tract is increasingly becoming one of the important habitats for human microbiota because the vaginal tract contains remarkably complex microbial communities¹.

Vaginal illnesses are among the most frequent gynecological issues. The vaginal microbiota's stability is influenced by a variety of variables. Age, menses, menarche, diseases, pregnancy, birth control, and sexual practices all affect the composition of the vaginal microbiota². Infections are a common occurrence in vaginal disorders. The human vaginal microbiota tends to play a crucial role in avoiding a variety of urogenital diseases, including bacterial vaginosis, yeast infections, sexually transmitted diseases, urinary tract, and HIV-related infections³. A significant number of cases of vulvitis, cervicitis, and pelvic infections are associated with urogenital diseases⁴. The healthy vaginal microbiota is dominated by the hydrogen peroxide-forming *Lactobacillus* spp.⁵⁻⁷, such as *Lb. crispatus*, *Lb. acidophilus*, *Lactocaseibacillus rhamnosus*, and others (except *Lb. iners*). This feature suppresses the growth of other organisms and excludes other bacteria unable to synthesize catalase⁷. Both healthy habitat and vaginal dysbiosis are often identified in the vaginal habitat of *Lb. iners*. It seems representative of a symbiotic or parasitic lifestyle, as opposed to other niche-flexible lactobacilli^{8,9}. Except for 9% of the strains¹⁰, *Lb. iners* are unable to produce hydrogen peroxide^{11,12}. However, facultative or obligate anaerobic bacteria, which are 100 to 1000 times more abundant than hydrogen peroxide-producing *Lactobacillus* spp., dominate a typical unhealthy vaginal flora^{13,14}. Furthermore, some non-infectious diseases, such as intrauterine adhesions, preterm birth, induced abortions, polycystic ovarian syndrome, miscarriage, uterine fibroid, infertility, and menstrual disorders, have been linked to microbial dysbiosis, represent a major threat to women's reproductive health¹⁵.

The function of many bacteria that are assumed "normal" within the vagina has been redefined thanks to the introduction of NGS technology. Scientists are concerned not only about potentially "harmful" bacteria but also about changes in the organization of the vaginal microbiota as a whole¹⁶. Although there are some disadvantages using this method, such as a lot of technical difficulties which need to be thoroughly studied and solved, and high costs, time-consuming protocols, NGS has managed to solve the drawbacks of conventional DNA sequencing approaches and find the use in a wide variety of applications¹⁷. NGS could also be applied effectively to classify a large variety of taxonomic species that would not be possible with other methods.

The present study aimed to identify bacterial vaginal microbiota using the NGS method and metagenomic approach at different taxonomic levels from the kingdom to the species level. Furthermore, the relationships of identified bacterial communities present in vaginal microbiota with age and marital status were determined by canonical correspondence analysis (CCA).

MATERIALS AND METHODS

Samples

In this study, a total of 38 vaginal swab samples were collected from patients admitted to Yeditepe University Hospital, Department of Obstetrics and Gynecology in June 2021, using the DNA/RNA shield collection tubes with a swab (R1107, Zymo Research, USA). The swabs were stored at -20 °C till DNA extraction. The information related to patients' age, marital status, preliminary diagnosis, and anamnesis status is given at Table 1.

The collection of all human materials was approved by Yeditepe University Clinical Research Ethics Committee (approval number: 1274, date: 20.08.2020).

DNA Extraction

Total DNA extraction was carried out using a ZymoBIOMICS DNA miniprep kit (D4300, Zymo Research, USA). The DNA

samples were quantitated spectrophotometrically by the Take3 plate of the microplate reader (Epoch-2, BioTek, USA). Then, DNA samples were stored at -20 °C up to amplicon PCR experiments for NGS.

NGS and Metagenomic Analysis

DNA library was prepared according to the 16S metagenomic sequencing library preparation guide instructions (Illumina, Inc., California, USA). In 16S rRNA amplicon PCR, the primer pairs F-primer: 5'-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG-3' and R-primer 5'-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC-3' were used. In total extracted DNA of vaginal swab samples, bacterial 16S rRNA V3-V4 regions were amplified by PCR using KAPA HiFi HS Mix (Roche, Germany). Then, the amplicons of each swab sample were indexed with dual indexes by the Nextera XT index Kit v2 Set-A (Illumina). All PCR products and indexed samples were cleaned using AMPure XP beads (Beckman Coulter, USA) in a magnetic rack (DynaMag™-96 Side, Invitrogen, Norway). The equimolar (10 nM) proportions of the samples were pooled in a tube, then it was diluted to 1 nM, and it was finally diluted to a 35 pM DNA library. The diluted library (20 µl) containing 5% (v/v) PhiX control DNA (Illumina) was loaded into an iSeq100 v1 cartridge (Illumina). The sequencing was performed in the iSeq100 system (Illumina) with a pair-end read type and two reads of 151 bp read length of the sequence.

The NGS data were analyzed using the 16S Metagenomics, Version: 1.1.0 software (Illumina). The sequence identity of clustered sequences by NGS was determined by an operational

taxonomic unit (OTU) approach. Alpha diversity values (Shannon species diversity index), the number of species, evenness, and taxonomic distributions of bacterial communities were determined by the 16S Metagenomics software Version 1.1.0 (Illumina) using RefSeq RDP 16S v3 May 2018 DADA2 32 bp taxonomical interference and the Ribosomal Database Project (RDP) Classifier¹⁸. CCA was applied using the PAleontological STatistics Software version 4.06b package (2021) to consider the variables of the patients' age and marriage status¹⁹.

RESULTS

In the present study, the swab samples for vaginal bacterial microbiota taken from 38 Turkish patients were evaluated. The patients' ages ranged between 22 and 46 years. Out of 38 patients, 21 of them were married, and 17 of the patients were single (Table 1). In addition, five of the patients applied for general control and no symptoms related to any diseases was observed (v2, v11, v22, v29, and v30) and they were considered healthy controls. A preliminary diagnosis of acute vaginitis was made only in one patient with pregnancy status (v35). Moreover, HPV with mild cervical dysplasia was prediagnosed in two patients (v7 and v13). Mastodynia with acute vaginitis was prediagnosed in three patients (v4, v5, and v10). Abnormal uterine and vaginal bleeding were prediagnosed in five patients (v3, v15, v16, v32, and v39). The remaining 22 patients were prediagnosed with acute vaginitis. Patient information with age, marital status, preliminary diagnosis, and anamnesis are given in Table 1.

The vaginal microbiota analysis was generated from a total of 2,047,376 high-quality NGS reads obtained from the total

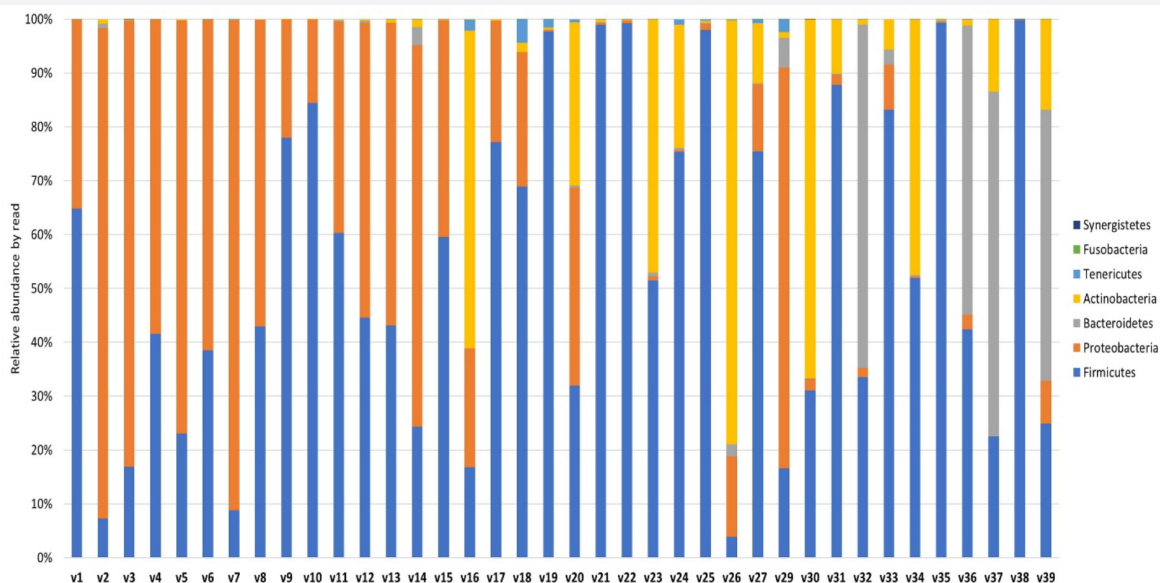


Figure 1. Relative abundance of bacterial communities at the phylum level determined by 16S metagenomic analysis

DNA of 38 vaginal swab samples and all belonged to the bacteria kingdom. The percentages of OTUs allocated to each bacterial phylum are given in Figure 1. Vaginal swab samples revealed the percent abundance of the top six phyla at the phylum level. The dominant phylum Firmicutes was followed by Proteobacteria, Actinobacteria, Tenericutes, Fusobacteria, and Synergistetes in the vaginal samples (Figure 1).

The percentages of bacterial OTUs assigned to the genus level were given in Figure 2. At the genus level, vaginal swab samples revealed the percent abundance of the top twenty genera. In addition, *Lactobacillus* was the most abundant genus in the vaginal swab samples, followed by *Prevotella*, *Enterobacter*, *Gardnerella*, and *Dialister*. The percent abundance of the

top twenty species was shown in Figure 3. *Lb. iners* was the most abundant species in vaginal swab samples, followed by *Gardnerella vaginalis*, *Enterobacter tabaci*, *Prevotella timonensis*, *P. bivia*, and *Lb. jensenii*.

The alpha diversity of the samples determined by Shannon species diversity index values and evenness is presented in Table 2. The lower evenness indicates the diverse vaginal microbiota. In this context, the highest diversity was found in v38 and v19 samples. The preliminary diagnosis of the v19 and v38 samples was acute vaginitis with vaginal discharge for 2 days. The lowest diversity was found in v39 and v36 samples. The preliminary diagnosis of the v36 sample was acute vaginitis with smelly vaginal discharge for 2 days and menstrual

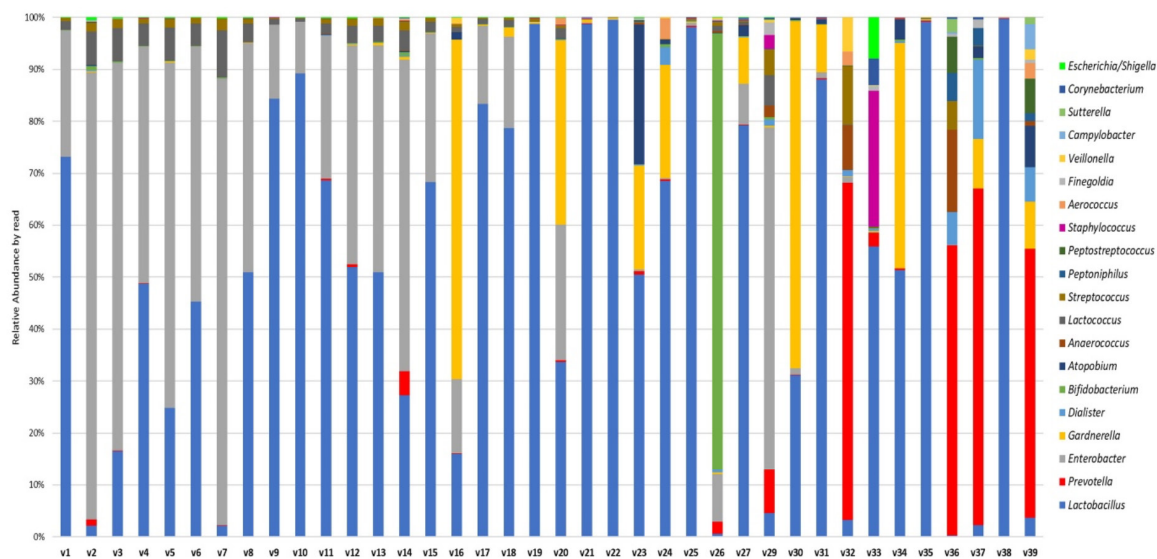


Figure 2. Relative abundance of bacterial communities present in the vaginal microbiota at the genus level

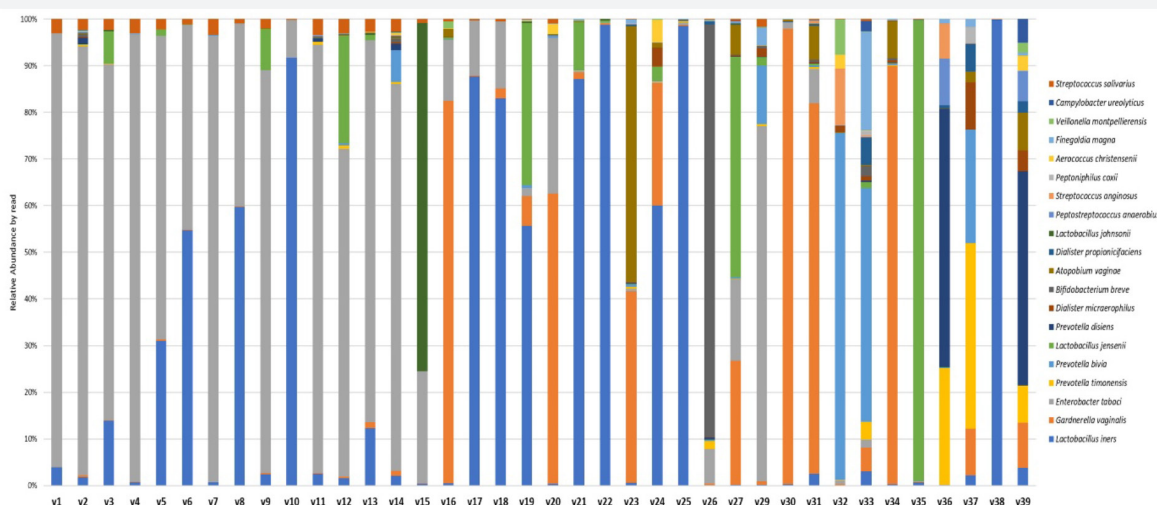


Figure 3. Relative abundance of bacterial communities at the species level

Sample ID	Age	Marital status	Preliminary diagnosis	Anamnesis
V1	29	Married	Acute vaginitis	Menstrual pain for 3 months.
V2	28	Married	Healthy	General control
V3	29	Married	Abnormal uterine, vaginal bleeding	Vaginal discharge for 2 days, Menstrual irregularity for 4 months.
V4	34	Single	Mastodynia, acute vaginitis	Vaginal discharge for 2 days. Pain in the breast.
V5	40	Married	Mastodynia, acute vaginitis	Vaginal discharge for 2 days. Pain in the breast for 1 week.
V6	36	Married	Acute vaginitis	Vaginal discharge for 2 days.
V7	27	Single	HPV with mild cervical dysplasia	Vaginal discharge for 2 days.
V8	46	Married	Acute vaginitis	Spotting in the vagina 4 days ago, Vaginal discharge for 1 week.
V9	31	Single	Acute vaginitis	Menstrual irregularity for 2 months
V10	41	Married	Mastodynia, acute vaginitis	Vaginal discharge for 2 days. 2 months delay in menstruation, anemia.
V11	33	Single	Healthy	General control
V12	30	Married	Acute vaginitis	Vaginal discharge for 2 days, Abnormal uterine bleeding for 2 months.
V13	36	Single	HPV with mild cervical dysplasia	Vaginal discharge for 2 days.
V14	31	Married	Acute vaginitis	Vaginal discharge for 3 months, Abdominal pain.
V15	41	Single	Abnormal uterine, vaginal bleeding	Vaginal discharge for 2 days, Menstrual irregularity for 2 months.
V16	35	Single	Abnormal uterine, vaginal bleeding	Vaginal discharge and itching for 2 days, Menstrual irregularity for 3 months.
V17	27	Single	Acute vaginitis	Vaginal discharge for 2 days.
V18	36	Single	Acute vaginitis	Vaginal discharge and bleeding for 2 weeks.
V19	41	Married	Acute vaginitis	Vaginal discharge for 2 days.
V20	28	Married	Acute vaginitis	Vaginal discharge for 2 days.
V21	28	Single	Acute vaginitis	Vaginal discharge for 2 days, uterine bleeding, Menstrual irregularity for 2 months
V22	32	Single	Healthy	General control
V23	36	Married	Acute vaginitis	Pain, burning, itching in the vagina for 2 days.
V24	36	Single	Acute vaginitis	Vaginal discharge for 2 days.
V25	41	Single	Acute vaginitis	Vaginal discharge for 2 days.
V26	37	Married	Acute vaginitis	Vaginal discharge for 2 days.
V27	22	Married	Acute vaginitis	Vaginal discharge for 2 days, 27-week premature birth and baby died.
V29	28	Married	Acute vaginitis	General control
V30	38	Single	Healthy	General control
V31	35	Married	Acute vaginitis	Vaginal discharge for 3 days.
V32	43	Married	Abnormal uterine, vaginal bleeding	Vaginal discharge for 2 days, Menstrual irregularity for 4 months.
V33	26	Single	Acute vaginitis	Vaginal discharge 1 week, Epigastric pain.
V34	32	Single	Acute vaginitis	Frequent urination and burning for 2 weeks, vaginal discharge for 1 week.
V35	32	Married	Acute vaginitis with pregnancy status	Vaginal discharge for 2 days.
V36	43	Married	Acute vaginitis	Smelly vaginal discharge for 2 days, Menstrual irregularity for 2 months.
V37	27	Single	Acute vaginitis	Vaginal discharge for 2 days.
V38	34	Married	Acute vaginitis	Vaginal discharge for 2 days.
V39	30	Married	Abnormal uterine, vaginal bleeding.	Menstrual irregularity for 4 months.

HPV: Human papillomavirus

Table 2. The number of NGS reads per sample, Shannon species diversity index, the number of identified species, and evenness values of the vaginal swab samples

Sample number	Sample ID	Number of reads	Shannon species diversity index	Number of identified species	Evenness
1	v1	59915	0.533	60	0.130
2	v2	15919	0.974	61	0.237
3	v3	25743	1.129	86	0.253
4	v4	32897	0.695	53	0.175
5	v5	47252	1.069	60	0.261
6	v6	49192	1.088	56	0.270
7	v7	41878	0.856	75	0.198
8	v8	24303	1.077	39	0.294
9	v9	69532	0.465	60	0.114
10	v10	142675	0.770	64	0.185
11	v11	22403	0.556	63	0.134
12	v12	73060	0.778	91	0.172
13	v13	12341	0.803	47	0.209
14	v14	8023	1.033	58	0.254
15	v15	38851	1.025	64	0.246
16	v16	17526	0.872	45	0.229
17	v17	46192	0.881	55	0.220
18	v18	37863	1.143	51	0.291
19	v19	86663	0.375	76	0.087
20	v20	30058	1.097	67	0.261
21	v21	42604	0.847	60	0.207
22	v22	26622	0.789	32	0.228
23	v23	21180	1.177	66	0.281
24	v24	50556	1.507	68	0.357
25	v25	27031	0.730	59	0.179
26	v26	36660	0.983	105	0.211
27	v27	68742	1.151	135	0.235
28	v29	19078	0.942	76	0.218
29	v30	83561	0.769	101	0.167
30	v31	51999	0.445	73	0.104
31	v32	54969	1.324	91	0.294
32	v33	31191	0.745	171	0.145
33	v34	67697	0.925	93	0.204
34	v35	115832	0.762	82	0.173
35	v36	93089	2.098	166	0.410
36	v37	236825	2.035	175	0.394
37	v38	46293	0.308	41	0.083
38	v39	91161	2.208	114	0.466

irregularity for 2 months, and the v39 sample was abnormal uterine and vaginal bleeding with menstrual irregularity for 4 months (Tables 1 and 2). In the vaginal samples, the number of identified bacterial species ranged from 32 to 175 (Table 2).

CCA is a correspondence analysis extension that uses direct gradient analysis²⁰. CCA was used to determine the associations between vaginal swab samples and their bacterial populations at the phylum, the genus, and the species levels, as well as their variables like marital status and age of examined patients.

The phylum points were presented in Figure 4A. In combination with the arrows for variables, it was accounted for 99.75% of the weighted averages of the 6 phyla of bacteria regarding the two variables. The sum of all eigenvalues was 0.03. Proteobacteria and Fusobacteria were mainly found in variable married/single with the highest percentages, whereas Actinobacteria and Tenericutes were found in variable age with the highest percentages. At the phylum level, a negative correlation was found between variables married/single status and age (Figure 4A).

The genus points were shown in Figure 4B. In combination with the arrows for variables, it was accounted for 99.69% of the weighted averages of the 20 genera of bacteria about the two variables, the sum of all eigenvalues being 0.10. *Campylobacter*, *Atopobium*, *Enterobacter*, and *Lactococcus* were mainly found in variable married/single with the highest percentages, whereas *Gardnerella* was found in the lowest percentages. *Anaerococcus*, *Streptococcus*, *Sutterella*, and *Veillonella* were mainly found in variable age with the highest percentages, whereas *Staphylococcus* and *Escherichia/Shigella* were found in the lowest percentages. In addition, a positive correlation was found between variables married/single and age at the genus level (Figure 4B).

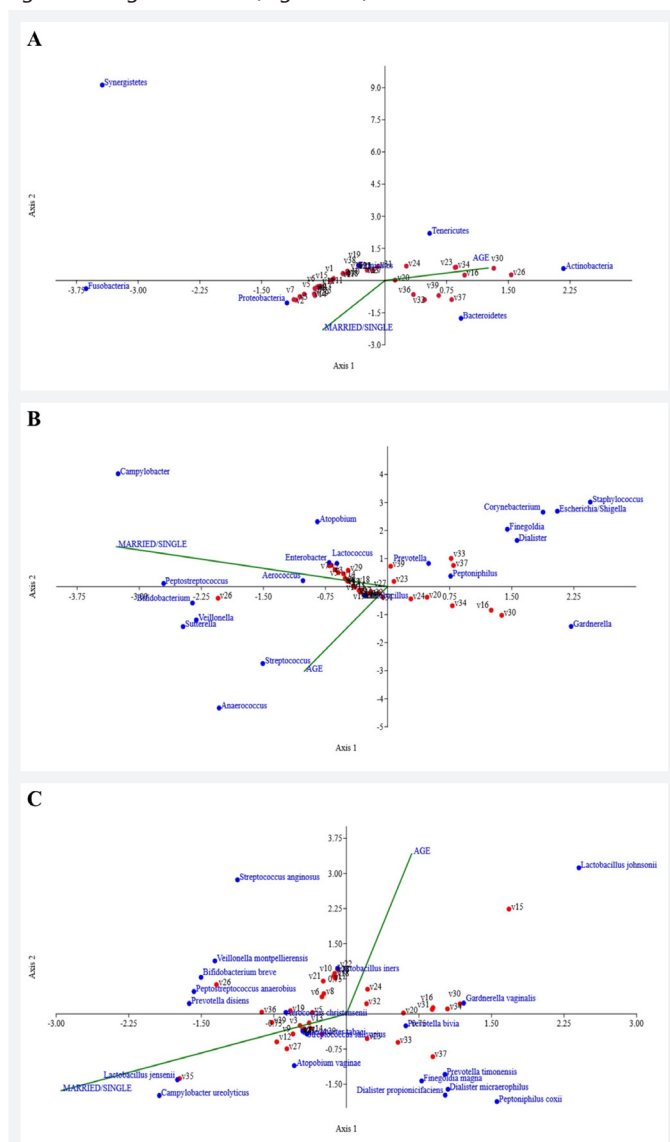


Figure 4. CCA results of the identified bacterial communities in the vaginal swab samples with respect to variables age and married/single status (A) at the phylum level, (B) at the genus level, and (C) at the species level

CCA: Canonical correspondence analysis

It was accounted for 99.42% of the weighted averages of the 20 species of bacteria regarding the two variables, the sum of all eigenvalues being 0.33. *Campylobacter ureolyticus*, *Lb. jensenii*, and *Atopobium vaginae* were mainly found in variable married/single with the highest percentages, whereas *Lb. johnsonii* and *Gardnerella vaginalis* were mainly found in variable age with the highest percentages. In addition, at the species level, a negative correlation was found between variables married/single and age (Figure 4C).

DISCUSSION

The human vaginal microbiome is complex, and researchers are only now beginning to understand its role in health and disease. The human microbiome is a collection of microorganisms like viruses, bacteria, and fungi that live in a symbiotic relationship with the human body²¹. The microbiome profile of each anatomical component of the body is unique. In the female vaginal tract, virus and bacterial profiles are complex, with a substantial inter-individual variation²².

Hočevár et al.²³ studied preterm delivery with 155 Caucasian women and they found the dominant phyla in the vaginal microbiota were Firmicutes and Actinobacteria, with lower contributions from Fusobacteria, Proteobacteria, and Tenericutes. At the genus level, the dominant members were *Lactobacillus*, *Gardnerella*, *Atopobium*, *Streptococcus*, and *Sneathia*. At the species level, *Lb. iners* and *Lb. crispatus* were most abundant bacteria. Their results were similar to our findings in the current study in which Firmicutes were the dominant phyla. However, we found Proteobacteria as the second dominant phyla, and Fusobacteria and Synergistetes were found to be the lower contributors for bacterial microbiota profile (Figure 1). Similarly, we found *Lactobacillus* was the most abundant genus. Indeed, in our study, *Atopobium* and *Streptococcus* were detected, but *Sneathia* was not found in our metagenomics study (Figure 2). At the species level, similarly, we found *Lb. iners* was the most abundant species. Indeed, we did not identify *Lb. crispatus* in our study (Figure 3). Many studies have detected that having *Lb. crispatus* in the vaginal area is connected with fine health; however, having *Lb. iners* in the vaginal area does not provide adequate protection against vaginal dysbiosis²⁴⁻²⁶. Exogenous bacteria are inhibited more effectively by D-lactic acid than by L-lactic acid. As a result, it appears that L-lactic acid makes *Lb. iners* less effective at preventing pathogen invasion²⁷. A recent study has reported that bacterial vaginosis patients exhibit vaginal colonization with a wide range of bacteria, including numerous previously uncultivated species that appear to be highly specific for bacterial vaginosis, as well as the absence of *Lb. crispatus*²⁸.

In a recent study, the microbiota of asymptomatic bacterial vaginosis patients was compared with that of healthy women

using NGS in India. Their results showed that *Lactobacillus* was dominant especially in normal healthy vaginal microbiota compared to dysbiotic microbiota with the abundance of *Gardnerella*, *Sneathia*, *Prevotella*, *Atopobium*, *Ureaplasma*, and *Dialister* genera²⁹. Similar to our results, *Prevotella*, *Gardnerella*, and *Dialister* were also identified with high read numbers. Furthermore, *Atopobium vaginae*, *Sneathia amnii*, *Mycoplasma hominis*, and *Prevotella disiens* were significantly demonstrated as biomarkers for dysbiosis, and *Lb. jensenii* as a biomarker for a healthy microbiota²⁹. The decrease in the number of protective *Lactobacillus* population in bacterial vaginosis patients leads to an increase *Gardnerella vaginalis* and *Prevotella species*³⁰. Indeed, *G. vaginalis* is the most isolated bacteria in bacterial vaginosis patients¹³. *Prevotella* spp. are associated with menopause, bacterial vaginosis, and body mass index (obesity), as well as they are the most heritable vaginal microbiota members among twins. Moreover, *Prevotella* spp. are negatively correlated with *Lactobacilli* and obese individuals have an abundance of *Prevotella* populations in their vaginal microbiota³¹.

The link between ethnicity and health is gaining attention in global health studies. Varied ethnic origins as Algerian women³², South African women³³, large North American cohorts consisting of four ethnic groups (Caucasian, African, Hispanic, and Asian)³⁴, Dutch, African Surinamese, South-Asian, Surinamese, Ghanaian, Turkish, and Moroccan women³⁵ have been documented in earlier research to have different geographical settlements and vaginal flora. The causes of these differences within ethnic groups are unknown, but they could be linked to genetic variations in innate and adaptive immune systems³¹.

In a prior study, Komesu et al.³⁶ discovered that *Lactobacillus* had the greatest connection with age. *Lactobacillus* content in vaginal microbiota was shown to be decreased as people became older, according to their research. The quantity of *Lactobacillus* has therefore been demonstrated to be age-dependent. Similarly, according to our CCA result related to the genus level (Figure 4B), we did not find a positive relationship with the genus *Lactobacillus*. In addition, *Anaerococcus*, *Streptococcus*, *Sutterella*, and *Veillonella* were mainly found to have a positive relationship with age variable. Dysbiosis, or changes in the microbiota, has been linked to reproductive failure, and changes in the microbiota may affect susceptibility to gynecological problems. For example, *Anaerococcus*, *Streptococcus*, and *Veillonella* were found in abnormal vaginal bacterial microbiota³⁷. *Sutterella* is a major component of the intestinal microbiota and plays an important role in the dysfunction of human microbiota³⁸. Previous results showed that marital status was significantly associated with vaginal bacterial microbiota and the incidence of vaginitis was shown to be more common in married women than in unmarried

women³⁹. Likewise, we also found the relationships between vaginal bacterial microbiota and marital status by using CCA in the present study (Figures 4A-C).

Study Limitations

The small number of patients in our study is a constraint. More research with a larger number of patients is required.

CONCLUSION

In conclusion, vaginal diseases continue to be a significant public health issue. Thanks to technological developments, it has been seen that the vaginal microbiota, which has been examined in more detail in recent years, is more complex than previously thought. It is critical to swiftly and precisely identify the bacteria involved in the etiology of vaginal diseases for proper therapy. Further studies are needed in more patients to confirm and develop current findings.

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Ethics

Ethics Committee Approval: All procedures used in studies involving human volunteers complied with the institutional and/or national research committee's ethical requirements, as well as the 1964 Helsinki Statement and its subsequent revisions or comparable ethical standards. The collection of all human materials was approved by Yeditepe University Clinical Research Ethics Committee (approval number: 1274, date: 20.08.2020).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.U., B.G.T., S.D., V.C.Ö., Design: S.U., M.S., B.G.T., S.D., V.C.Ö., Data Collection or Processing: S.U., M.N.Z.Y., B.B.T., E.E.A., B.G.T., S.D., Analysis or Interpretation: S.U., M.S., M.N.Z.Y., B.B.T., E.E.A., Literature Search: S.U., Writing: S.U., M.S., V.C.Ö.

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Experiences of Nurses Working in the Neurosurgery Clinic on Communication Difficulties with Patients Having Brain Tumors: A Qualitative Study

Nöroşirurji Kliniğinde Çalışan Hemşirelerin Beyin Tümörü Olan Hastalar ile Yaşadıkları İletişim Güçlüklerine İlişkin Deneyimleri: Nitel Bir Çalışma

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ABSTRACT

Aim: Effective communication between patients and nurses is the basic indicator of the quality of nursing care and is a patient safety issue. It is even more important in patients who are at high risk of having communication problems due to some conditions such as brain tumor, or have limitations in this regard. This study was conducted to determine the experiences of neurosurgical nurses on their communication difficulties and coping methods while providing care for patients with brain tumors.

Materials and Methods: This study was planned as a qualitative research conducted with the interpretative phenomenological analysis method. In-depth, face-to-face individual interviews were conducted with 10 nurses determined through purposive sampling method.

Results: The results were discussed in three groups: communication difficulties experienced by nurses, coping methods, and solution suggestions. Regarding the communication difficulties of nurses, the main themes and sub-themes of patient-related factors and institution-related factors were determined.

Conclusion: It was observed that the situations in which nurses had communication difficulties and the reasons for them were multidimensional. It was determined that nurses mostly used therapeutic communication methods to solve the communication difficulties and coped with individuals' problems by meeting their care needs; however, it sometimes turned to non-therapeutic communication.

Keywords: Brain tumors, communication, neurosurgery, nursing

ÖZ

Amaç: Etkili hasta-hemşire iletişimi hemşirelik bakımının kalitesine ilişkin temel bir gösterge ve hasta güvenliği konusudur. Etkili iletişim, özellikle beyin tümörü gibi iletişim sorununa yol açma riski yüksek olan rahatsızlıkları olan veya bu açıdan sınırlılık yaşayan hastalarda daha da önemlidir. Beyin tümörü olan hastaların hemşirelik bakımında bireyselleştirilmiş ve bütüncül bir yaklaşım ile terapötik iletişim sürdürülmelidir. Ancak, bakım sürecini etkileyen çeşitli nedenler bu süreci olumsuz yönde etkileyebilir.

Gereç ve Yöntem: Bu araştırma, nöroşirurji hemşirelerinin beyin tümörü olan hastalara bakım verirken yaşadıkları iletişim güçlükleri ve baş etme yöntemlerine ilişkin deneyimlerini belirlemek amacı ile yorumlayıcı fenomenolojik analiz yöntemi ile gerçekleştirilen nitel bir çalışma olarak planlandı. Amaçlı örnekleme yöntemi ile belirlenen 10 hemşire ile derinlemesine, yüz yüze bireysel görüşme yapıldı.

Bulgular: Elde edilen bulgular hemşirelerin yaşadıkları iletişim güçlükleri, baş etme yöntemleri ve çözüm önerileri olmak üzere üç grupta ele alındı. Hemşirelerin yaşadıkları iletişim güçlüklerine yönelik hasta ile ilişkili faktörler ve kurum ile ilişkili faktörler ana temaları ve alt temaları belirlendi.

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Baş etme yöntemleri ile ilişkili olarak; terapötik ve terapötik olmayan yöntemler ana temaları saptandı. Çözüm önerilerinin ise, terapötik bakım ortamının güçlendirilmesi ve hemşirenin güçlendirilmesi temaları altında toplandığı görüldü.

Sonuç: Hemşirelerin iletişim güçlüğü yaşadığı durumların ve nedenlerinin çok boyutlu olduğu görüldü. Hemşirelerin iletişim güçlüğü ile baş etmede çoğunlukla terapötik iletişim yöntemlerini kullandığı ve bireyin bakım gereksinimlerini karşılayarak sorunları ile baş ettikleri ancak zaman zaman terapötik olmayan iletişime yöneldikleri belirlendi. Hemşirelerin yaşadığı iletişim güçlüğünü azaltmaya ilişkin önerilerin hayata geçirilmesi için mesleki faaliyetler ile kurumsal düzenlemeler gerektiği saptandı. Araştırmadan elde edilen bulguların, hemşirelerin yaşadıkları iletişim güçlüklerinin azaltılması/ortadan kaldırılmasında hemşirelere ve çözüm stratejilerinin belirlenmesinde yöneticilere rehberlik edeceği düşünülmektedir.

Anahtar Kelimeler: Beyin tümörü, iletişim, beyin ve sinir cerrahisi, hemşirelik

INTRODUCTION

Communication is defined as the transfer of knowledge, meanings and feelings through verbal and non-verbal ways^{1,2}. Communication is the most basic building block of nursing and is a dynamic process that lasts from the moment of first encounter with the patient to the moment of the end of care because nurses cannot fulfill their main roles such as physical care, education, and emotional support without communication^{3,4}.

It is very important for nurses to have nursing knowledge and experience and also to evaluate individuals holistically so that they can communicate effectively with the individuals for whom they provide care^{1,5}. Brain tumors, as one of the diseases that may affect the maintenance of life, may lead to different physiological and psychological consequences in individuals. Patients, their families and healthcare team members face a progressive, worsening process⁶. This process extending from diagnosis to treatment is quite tiresome. Furthermore, depending on the region of the brain affected by the tumor, the problems in perception, motor and sensory functions, disability, memory and perception impairment, mental and behavioral problems, speech and communication problems may occur^{7,8}. Nevertheless, in addition to loss of speech and hearing, the losses in other gesture, mimic and motor functions that support verbal communication in patients with brain tumors cause healthcare team members to have communication difficulties with the patient⁹. The failure of healthcare professionals to allocate enough time for the patients with sensory and motor loss, the lack of information about providing and maintaining non-verbal communication with the patient, the failure to apply visual communication techniques, and the problems arising from the clinical environment make communication with the patient even more negative^{1,10,11}. On the other hand, the care of neurosurgical patients requires a nurse-centered team approach¹². When the relevant literature is reviewed, it is indicated that nurses mostly have communication difficulties with the patients hospitalized in oncology and neurology clinics, intensive care units, emergency departments, and elderly care clinics and with the patients diagnosed with dementia^{11,13,14}. Despite the limitations that occur in patients due to brain tumor, effective communication is very important in planning individual needs. In patients with brain tumors,

psychosocial interventions are needed to reduce the cognitive effects of the disease and anxiety¹³. To cope with the changes in sensory functions is possible with effective communication and accurate information¹⁵. Although a limited number of studies examining the difficulties experienced by nurses providing care for patients with brain tumors were reached in the literature, no study on the communication difficulties experienced by nurses was found. Therefore, this study was planned to evaluate the communication difficulties experienced by neurosurgical nurses while providing care for patients with brain tumors, and the factors affecting them.

MATERIALS AND METHODS

Study Design

This study is a qualitative study conducted with the interpretative phenomenological analysis method to explain the experiences of nurses working in the neurosurgery clinic on their communication difficulties with patients having brain tumors. Phenomenological studies aim to create a common meaning for individuals with the same experience on a concept or phenomenon. Interpretative phenomenological qualitative studies are a way of interpreting and understanding the experiences of individuals¹⁶. Interpretative phenomenology focuses on the subjective experiences of individuals and groups. This approach aims to reveal experiences¹⁷.

Participants

Ten nurses with at least 2 years of experience in the field of neurosurgery, who worked in a neurosurgery clinic and agreed to participate in the study, were included in the study. While the mean age of nurses was 33.8±6.19 years, 80% of them had bachelor's degree, the mean working experience was 10.6±6.23 years, and the duration of working experience in the field of neurosurgery was 7.8±7.02 years.

Data Collection

Data were collected using face-to-face, semi-structured in-depth individual interview technique between February and September 2016. The mean duration of the interviews was 50 minutes. Some warm-up questions such as "What are your experiences on communication difficulties with patients

having brain tumors?", "What are the factors affecting your communication difficulties with patients having brain tumors?", "Which methods do you use to cope with communication difficulties?" and "What are your suggestions for preventing and resolving communication difficulties?" were used to detail the nurses' experiences. Each interview was recorded, short notes were used for important points during the interview, and the data were written word by word.

Data Analysis

Descriptive statistical methods (mean, percentage) were used in the analysis of the individual characteristics of the nurses. Colaizzi's seven-step method for data analysis, which is commonly used in phenomenological research, was used for the analysis of the data obtained from the interviews. This method involves the process of understanding and formulating the data and creating theme sets. In order to check the accuracy of the results obtained, they were presented to the participants and their approval was obtained¹⁸⁻²⁰. After the data were analyzed separately by two researchers, they were shared with other researchers and the themes were finalized by reaching a consensus. After analyzing the data, the emerging themes and comments were shared and verified to ensure their validity and reliability.

Ethical Considerations

Ethical approval from İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (protocol no: 45977, date: 05/02/2016), and permission from the institution where the study was conducted were obtained to conduct the study. Nevertheless, researcher informed the participants about the aim of the study, the roles of the participants, the benefits and possible risks of the study, withdrawal from the study at any time, and the privacy of information. Verbal and written permissions were obtained. In the direct quotations in the results, the nicknames specified by nurses were used instead of their real names. The sound recordings were only listened and written down by the researchers and were not shared with anyone else.

RESULTS

As a result of the data analysis, the results were grouped under 3 sub-headings, including communication difficulties experienced by nurses, coping methods and solution suggestions. 2 main themes related to communication difficulties experienced by nurses, 2 main themes related to coping methods, and 2 main themes for the solution suggestions were determined. The results are discussed and explained in detail below. The main themes and sub-themes of communication difficulties experienced by nurses, coping methods and solution suggestions are presented in Table 1.

Communication Difficulties Experienced by Nurses

In the in-depth individual interviews, two main themes and sub-themes, including the patient-related factors and institutional factors, were determined for the difficulties of nurses with patients having brain tumors. While the sub-themes of individual characteristics of the patient, attitudes of patients' relatives, patient's lack of information and patient's perspective on nursing were determined for the main theme of patient-related factors, the sub-themes of institutional opportunities and collaboration of healthcare team members were determined for the main theme of institutional factors.

Theme 1: Patient-Related Factors

Sub-theme 1: Individual characteristics of the patient

Nurses stated that they had communication difficulties due to the patients' age, educational status, lack of knowledge of Turkish, psychological state, and the physiological effects of the disease on the individual.

The statements including the experiences of the 2 nurses who participated in the study on the educational levels of patients are as follows;

"Patients think that they know better and what we do is wrong because of their higher education." (Nickname: Daisy).

"You cannot communicate with those with no education on many issues. They try to do something for their patients as they wish or they don't understand us. We give information about the nutrition of their patients, they think nothing would happen. For example, I say let's start nutrition 4 hours after the operation, they ask 10 more people when to feed, other than me." (Nickname: Cat).

The nurses stated that the patients had communication difficulties because of the lack of knowledge of Turkish. The statements of 2 nurses on this subject are as follows;

"We have a patient in number 2 who does not speak any Turkish. Normally, when I administer the medicine, I ask the patient if he/she is nauseous. I cannot ask it to the patients who do not speak a language, I look at their facial expression. I wonder if their facial expression change." (Nickname: Sun).

"I have a patient who speaks Arabic, I cannot communicate with my patient." (Nickname: Rose).

The nurses stated that they had problems such as patients' introversion, pessimistic mood, anger, fear, anxiety, depressive mood, impaired self-perception, and rejection of treatment due to the psychological effects of the disease, and communication difficulties associated with them. Meeting the expectations of the patients during the treatment process and the reactions of their relatives affect the psychological state of the patients.

Table 1. Main themes and sub-themes of communication difficulties experienced by nurses, coping methods and solution suggestions	
Main themes	Sub-themes
Communication difficulties	
Main theme 1. Patient-related factors	Individual characteristics of the patient Attitudes of patients' relatives Lack of informing the patient Patient's perspective on nursing
Main theme 2. Institution-related factors	Institutional opportunities Collaboration of healthcare team members
Coping methods	
Main theme 1. Therapeutic methods	Maintaining therapeutic communication Establishment of a therapeutic setting
Main theme 2. Non-therapeutic methods	Meeting the care needs
Solution suggestions	
Main theme 1. Establishment of the therapeutic care setting	
Main theme 2. Strengthening of the nurse	

The statements of the nurses regarding this sub-theme are as follows;

"They are very anxious. They ask about their dressing, when will our dressing be done, do we have medication, when will you give my painkillers? Although we tell them about every treatment, they still ask again and again. Because pain is already a bad thing, and brain surgery is difficult, so of course, they start to ask more and more" (Nickname: Sun).

"Sometimes they do not hear anyone, say something as much as you want, they are in their own world. Say what you want, explain what you want. Whenever something begins to go well, even moving the finger and even a little use of their hand energize them, and they make sense with what we say." (Nickname: Sun).

"Patients may be disappointed after surgery. Crying crisis, not speaking, patients who can speak, we know they speak, but they do not speak, they do not communicate eye to eye." (Nickname: Sun).

"One of our patients is depressed because of staying for a long time, he is constantly crying, is conscious but does not speak. Since he has a tracheostomy, he points out his pain with signs, we suggest him to write on paper with movements when he needs toilet, but he does not obey the orders because he is depressed and agitated." (Nickname: Rose).

"One of our patients is conscious, cannot speak, the patient's relative is constantly complaining, gets angry with the patient, cannot accept this situation, which affects the patient's psychology. The patient is always nervous, there was an attempt to attack my friend yesterday, there may be such situations, and of course it affects our motivation." (Nickname: Freedom).

The nurses who participated in the study stated that they had communication difficulties due to brain tumor-related dysphagia, aphasia, impaired consciousness, presence of tracheostomy, impaired perception, loss of motor and muscle functions, vision, hearing loss, seizure, pain and insomnia. The statements of 2 nurses regarding the physiological effects of the disease are as follows;

"Especially disoriented patients do not accept care. They cannot perceive what we say."(Nickname: Sun).

"There may be pain, sleep problems, fears about surgery in younger patients." (Nickname: Rose).

Sub-theme 2: Attitudes of patients' relatives

The nurses indicated that patients' relatives caused difficulties in communicating with the patient during the care process. It was determined that conflicts with patients' relatives made it difficult to maintain the patient's care and negatively affected communication with the patient. The statements of the nurses on their communication difficulties are as follows;

"When the patient vomits or when the patient has a tendency to sleep, a sudden change occurs, the relatives of the patient are stressed too much, get angry and reflect it to us. They are constantly expecting from us to be with their patient." (Nickname: Rose).

"Contact isolation was applied in one patient due to the growth of Klebsiella. The relative of the patient thinks that I have infected his patient, and according to my observation, he wants to get revenge against it. With gloves in his hand, he touches our counters, touches the door handle of our room, and argues with us when we warn him. Because when we cannot coordinate the patient's relatives, we cannot coordinate the situations related to our patient. We have

trouble, patient relatives reflect all crises to us and we cannot find a solution." (Nickname: Rose).

"When we have a patient who does not know his disease, the patient's relatives say that our patient does not know what happened, please do not reveal it, we told him that he was hospitalized for examination. At first step, we try not to tell the patient about his diagnosis. However, we also tell patient's relatives that it is not true, we should tell your patient about it. By explaining that this process is temporary and that he is here for recovery, we raise the awareness of both the patient and the patient's relatives and make them sleep more comfortably." (Nickname: Fish).

"We have problems especially with patient relatives. Many of our chronic patients are unconscious and cannot express themselves. However, patient relatives may prevent us from providing care. They cannot accept the situation. When the care of the patient is left to one person, patient relatives are also sleepless and nervous." (Nickname: Freedom).

"We may have problems with our patients with tracheostomy. While aspirating, the relatives of the patients may consider that we are drowning the patients and leaving them out of breath. Sometimes they interfere with this situation, so we have problems. If discharge is planned, we should provide training on nutrition and aspiration, they do not want to admit it, they say they can do anything but never be able to perform aspiration." (Nickname: Cat).

Sub-theme 3: Lack of informing the patient

The nurses indicated that the lack of information was an important factor in their communication difficulties with patients. The statements of a nurse on this issue are given below.

"Physicians do not go into much detail about the patient's condition, and when the patient has sequelae after surgery, patients and also thire relatives may go against us by shouting why I am in this state or constantly asking for something, and the patients who cannot speak do it with gestures." (Nickname: Fish).

"Materials are requested during the surgery, and some tools such as tips, blades, microscope materials compatible with the devices are used. These are the necessary materials for a successful operation. These products are unfortunately not covered by health insurance. Patients are therefore required to pay some fees. The patients sometimes have difficulty to understand why these fees are asked to be paid. It is necessary to inform patients and their relatives to the last detail before the surgery. When patients cannot understand these situations, it is up to us to explain it in a way that the patient can understand." (Nickname: Fish).

Sub-theme 4: Patient's perspective on nursing

The nurses indicated that the society's perspective on nursing profession affected them to have communication difficulties. It was determined that the perspective of the patient's relatives on nursing together with the patient was important in experiencing communication difficulties. The statements of the nurses on this sub-theme are as follows;

"When we say that we have a lot of work right now and will be right there, they immediately respond by stating 'but my patient is waiting, my patient will stand up'. However, they do not reflect too much stress on doctors as much as they do to us. In fact, they are constantly asking us the questions they should ask them. While some of them value nurses very much, some of them consider nurses simpler, I perceive it. I think that people who have a significant difference in their behaviors towards nurses and doctors have a negative perspective on nurses." (Nickname: Rose).

"What annoys me the most is that they consider nurses worthless. Some patients think that they can shout, they have everything, they can get angry, nurses have to do all of them. There is not any work on this issue, an also the hospital administration... People think that they have all rights. They think that they can shout to the nurse as they wish. We are so worthless in the eyes of some patients' relatives, this is what affects me the most (crying)." (Nickname: Freedom).

"Sometimes communication problems with doctors can be reflected to us. We may also have problems with dressings after surgery. They cannot say anything to the doctors about why they pulled the tapes fast while dressings and why they act like that, they feel the need to tell us since they find us closer to them. To be honest, there are also people who I think are saying it sometimes in bad faith, they reflect their problems to us to explain them by stating even the smallest thing they experienced in the hospital, for instance, channels on the TV or having no reception." (Nickname: Cat).

Main Theme 2: Institution-Related Factors

It was determined that institution-related factors affected nurses to have communication difficulties with patients. For the main theme of institution-related factors, the sub-themes of institutional opportunities and collaboration of healthcare team members were determined.

Sub-theme 1: Institutional opportunities

It was determined that nurses experienced communication difficulties due to patients and their relatives requesting to go to different units outside of the clinic for laboratory and other examinations, questioning and rejecting in case of lack of material and equipment and when the missing materials are met by patients, the delay of treatments or postponement

of surgery because of insufficient physical conditions and healthcare personnel, and the lack of interpreter support for patients who did not speak the language. The statements of the nurses on this theme are given below.

"It is difficult for the relatives of the patients to take care of the chronic patient, to stay with them day and night and to adapt to the hospital conditions. The fact that the laboratory and imaging center are in the main building and we are in a separate building, and the fact that they have to go outside the building for blood samples and other imaging procedures negatively affect our communication. This process also causes us to get more tired in the same way." (Nickname: Freedom).

"Some materials may not be present due to the terms of purchase from time to time. In particular, it may take time to supply expensive drugs and to complete the consultation process for reported drugs" (Nickname: Fish).

"Recently, we have received interpreter support for a few patients. However, interpreter is not always with you" (Nickname: Sun).

Sub-theme 2: Collaboration of healthcare team members

The nurses stated that the problems experienced in the collaboration of healthcare team members might affect their communication difficulties with the patients. The difficulties related to this theme were determined as physicians' incomplete information/not informing nurses about the care and treatment processes of patients, failure to provide a professional work environment in cases where auxiliary staff disrupted their duties and responsibilities, and nurses having difficulty and feeling lonely from time to time when there were communication problems with patients and relatives. The fact that nurse received information from the patient when physicians did not inform them was also considered as an important problem. Some statements of the nurses on this theme are given below.

"Sometimes, physicians include the patient in the surgery list, which causes us to learn the patient to be operated late since the lists are not updated quickly. Therefore, it affects the patient's oral feeding." (Nickname: Wind).

"Even if you are right you may not be able to speak, we have difficulty in defending ourselves in case of exposure to any form of violence, such as the patient's condition or working conditions, and experiencing such things makes you feel lonely." (Nickname: Wind).

Coping Methods

The nurses were asked what coping methods they used when they had communication difficulties with patients. Two main themes and sub-themes, therapeutic and non-therapeutic methods, were determined for coping methods.

Main Theme 1: Therapeutic Methods

It was determined that the nurses who participated in the study mostly used therapeutic methods when they had communication difficulties with their patients. For this theme, the sub-themes of maintaining therapeutic communication, establishment of a therapeutic setting, and meeting the care needs were determined.

Sub-theme 1: Maintaining therapeutic communication

It was determined that the nurses maintained therapeutic communication to deal with cases where they had communication difficulties with patients. In this context, they stated that they used various therapeutic methods to strengthen communication with patients who had difficulties in hearing, speech and perception or in maintaining communication due to psychological reasons. Some statements of the nurses on this sub-theme are given below.

"If the patient cannot speak but write, we ask him to write. If the patient has a partial hearing loss, we try to speak loudly, or if he does not hear at all, we try to understand the expressions by showing the alphabet. The patient with tracheostomy cannot express himself by speaking, but after a while, we communicate by lipreading. If he does not see it, we let him touch because the patient wants to feel safe." (Nickname: Blue).

"In functionally inadequate patients, we communicate by touching, eye-to-eye communication, and even just with the finger. Each patient has his own communication. We can understand some patients with their finger and others by blinking an eye. Even with his eyebrow, we know which way he will turn." (Nickname: Sea).

"When patients feel panicked, we try to be revealing to them and we calm them down. Then, we go to the patient and talk to them more. For instance, when the patient has a seizure, we talk to them more and take time to communicate. After a while, their panic reduces, we see that their perspective towards us is also more moderate and their confidence increases." (Nickname: Rose).

Sub-theme 2: Establishment of a therapeutic setting

It was determined that the nurses coped with communication difficulties by establishing a therapeutic setting and supporting the patients' self-expression and coping with stress. Accordingly, they indicated that they performed interventions such as supporting the individual's participation in the care process, orientation to the service, seeking interpreter support for patients not speaking the language, and strengthening communication with the patient's family/relatives. Some statements on this sub-theme are given below.

"We introduce the service and provide training on service orientation such as mealtime and visitor restrictions" (Nickname: Wind).

"We observe the patient. For instance, does he eat his own food? If he has the strength to hold the spoon and the glass, I say you can shake my hand. I say hold your glass and drink by yourself. When he regains his self-confidence, he relaxes psychologically and communicates better with us." (Nickname: Sun).

Sub-theme 3: Meeting the care needs

The nurses who participated in the study indicated that they coped with communication difficulties more easily when they met their patients' care needs. They stated that it was effective to meet their care needs through nursing interventions such as relieving the pain of a patient, performing supportive interventions for sleeping in case of a problem in falling asleep or sustaining sleep, ensuring safety in case of seizures, or providing emotional support when they felt psychologically unwell. The statements of a nurse on this issue are as follows;

"When we support a patient with pain through interventions such as positioning, reducing the lights, and enabling him to listen to music, his trust in us also increases and our communication gets stronger." (Nickname: Sea).

Main Theme 2: Non-Therapeutic Methods

It was observed that nurses sometimes used non-therapeutic methods along with the therapeutic methods when they had communication difficulties. It was determined that when the nurses had communication difficulties, they exhibited improper communication behaviors such as restricting communication with the patient individual, using the language of conflict, blaming, and reproaching the patient's behavior with inappropriate sexual content. The statements of some nurses are given below.

"I sometimes say the patient that he/she is not happy; if you are not happy, then I will not come to the room." (Nickname: Sun).

"If the patient or his relative communicates with us in a very disrespectful and bad manner, we try not to spend too much time in that room. Because as the event grows, we are exposed to physical violence, so we restrict communication and deal with it in that way. Of course, there is no restriction on his care." (Nickname: Wind).

"The patient or his relative shouts and gets angry, we try to soothe them properly, but of course, when the occasion arises, people may be out of patience. There are also cases where the nurse reacts. At one point, people may not be patient. Being unjustly insulted and attacked, of course, also try one's patience." (Nickname: Freedom).

"Some patients behave abusively if the frontal region is affected. Next to her wife, they say nurse lady is very beautiful, let's go out to dinner and propose to marriage. We say words like

'it does not suit you at all' " (Nickname: Blue).

Solution Suggestions

The nurses who participated in the study were asked about their solution suggestions to prevent communication difficulties with patients and to strengthen communication. For solution suggestions, the themes of establishment of the therapeutic care setting and strengthening of the nurse were determined.

Main Theme 1: Establishment of the Therapeutic Care Setting

The nurses indicated that by strengthening the therapeutic care setting, communication difficulties could be prevented and the problems could be solved. To this end, suggestions were made on nurse's empathy and approach with a professional language, informing the patients and their relatives by the nurse regularly, informing the patients and their relatives by physicians, informing nurses by physicians, organizing educational seminars/meetings for the patients and their relatives, providing regular psychological support to patients and their relatives in the process of accepting the disease, regulation of the number and ratio of patients/nurses, solving the material supply, patient referral and insurance problems, and adopting a professional approach in the relations with auxiliary staff. Some statements of the nurses are given below.

"At school, we have learned to put oneself in the patient's shoes or in the patient's relative's position. Empathizing. If we can really do it, I think we can solve everything." (Nickname: Sun).

"Psychological support can be provided to patients and their relatives. Training can be provided for the relatives of patients. There are meeting rooms, meetings can be held. Information can be given, moral support can be given." (Nickname: Freedom).

"Physicians should inform the patients and their relatives. In every respect, for instance on drugs, information given before and after may be a solution." (Nickname: Fish).

Main Theme 2: Strengthening of the Nurse

The nurses indicated that they needed motivating factors to deal with the situations where they had difficulties and to solve the problems. In this context, they stated that organizing regular and interactive in-service trainings, strengthening professional solidarity, institutional support of nurses, organizing social activities with managerial support and motivation would contribute to the strengthening of nurses. Some suggestions of the nurses are given below.

"An information symposium can be held. No matter how much we follow, we need to participate in more activities about how to approach such patients" (Nickname: Sea).

"I think we need training all the time. We improve ourselves through in-service training programs. Interactive trainings would be more effective." (Nickname: Wind).

"Getting psychological help may be important for strengthening communication." (Nickname: Blue).

"I think we can deal with problems more easily if we cooperate with nurses and if physicians also support." (Nickname: Wind).

DISCUSSION

Communication is a complex and multidimensional process, and human responses are decisive in maintaining the communication. In the clinical setting, nurse-patient communication is also affected by the individual's responses⁶. Awareness of the patient's responses to the disease and treatment/care process is essential for maintaining effective communication and providing quality care. In this context, nurses are expected to turn to therapeutic and individual-centered communication^{3,4}. In particular, physical, psychological and social changes experienced in patients with brain tumors should be addressed with a holistic perspective, and a multi-faceted approach should be adopted^{12,21}. In a study conducted with patients with brain tumors, it was reported that communication was one of the most important indicators of the quality of care²². In this study conducted based on this information, it was aimed to reveal nurses' experiences on communication difficulties with patients having brain tumors.

In the interviews conducted with the nurses within the scope of this study, it was observed that their experiences on communication difficulties were gathered under two main themes, namely patient-related and institution-related. The sub-themes of individual characteristics, patient relatives, lack of information and perspective on nursing determined in relation to diseased individuals revealed that communication was affected in a multidimensional way. Studies demonstrated that patients diagnosed with brain tumors frequently experienced high levels of distress, including emotional and physical problems such as depression, insomnia, fatigue, pain, constipation, difficulty in concentrating, for reasons such as the presence of functional disorders and negative prognosis²³. Similarly, in this qualitative study, it was determined that psychological state and the experiences regarding the physiological effects of the disease on the individual caused communication difficulties. The nurse should diagnose the possible and current problems in the individual by making a comprehensive nursing diagnosis from the first moment he/she meets the patient. Thus, the nurse will evaluate the patient and their relatives with a holistic perspective and recognize their needs at the earliest time, and possible problems will

be avoided^{24,25}. This diagnostic process can make a significant contribution to preventing possible communication difficulties.

While carrying out the caregiver roles of diseased individuals and their relatives, nurses should be aware that they may experience depression, anxiety, and mental health problems. Patients' relatives may consider that they are sometimes unable to cope and are left alone while providing care to this individual with a high level of addiction. In this regard, the health care professional should evaluate the individual with himself/herself and his/her environment and continue his/her care with a holistic perspective²⁶. It should be accepted that anxiety and fear reactions of individuals are normal¹². The experiences revealed by this study demonstrated the importance of including the individual and their family in the care as much as possible and the family centered care approach. Based on this information, the establishment of a reliable and calm communication environment for providing psychosocial support to patients and their relatives and the adoption of effective communication methods constitute the basis of nursing practices^{27,28}.

Failure to adequately meet the information needs of patients with brain tumors is an important problem^{21,29}. However, giving information is also a way of involving the individual in his or her care process²². The reasons such as occasional intense work, long working hours and large number of patients significantly affect the communication. The fact that the hospital where the study was conducted was a university hospital and the presence of a single neurosurgery clinic, and insufficient number of specialist physicians working in the relevant clinic led to disruptions in the patient-nurse-physician communication in institutional factors. Furthermore, the risks of the interventional procedures to be performed disturb the relatives of the patients nervous and cause an increase in the expectations from the healthcare professionals. Accordingly, the functionality of comprehensive and systematic information processes of patients and their relatives regarding all effects of the disease and the treatment/care processes can make significant contributions to the solution of problems^{21,30}.

The perspectives and attitudes of patients and their relatives towards the nursing profession are also affected by the socio-cultural factors experienced. This theme was also identified as one of the barriers in nurse-patient interaction in the qualitative research conducted by Arkorful et al.³¹. It may be suggested that nurses, professional organizations and administrations should conduct information and awareness studies so that the society would develop a positive perspective on nursing profession. It may be useful to clarify the duties and responsibilities of health professionals at the institutional level and to declare/announce them in a way that patients/their relatives can see and reach.

Another factor affecting nurses to have communication difficulties is the institution-related factors. The sub-themes of institutional opportunities and collaboration of healthcare

team members were determined for this main theme. When the experiences of the nurses on this theme were examined, it was observed that there was a need for structural changes for the solution of problems related to the institutional infrastructure. On the other hand, the fact that nurses are the team members to whom patients and their relatives communicate their problems and from whom they expect solutions can also be considered as an indicator of their easier communication with nurses and their belief that nurses can produce solutions. It can be said that the continuous presence of the nurses in the clinical setting and their open communication with the patient/relatives affected this situation. This situation, which is defined as a communication difficulty, can also be considered as an indicator of the trust of patients/their relatives in nurses.

Nowadays, the importance of a multidisciplinary team approach in health care settings is emphasized. Open and effective communication and collaboration among healthcare team members have a key role in the management of treatment and care processes³². Team communication is also an issue of safety in healthcare^{33,34}. In this study, it was demonstrated that the problems experienced in the collaboration of healthcare team members were effective in communication difficulties with patients/their relatives. Accordingly, it may be useful to organize activities (scientific, social, educational, etc.) for the effective communication of the healthcare team, collaboration, determination of workflows for taking responsibility in accordance with the job/job descriptions, organization of in-service trainings, and the adoption of the concept of team.

When nurses' experiences of coping with communication difficulties were examined, two main themes, therapeutic and non-therapeutic methods, were determined. It was stated that therapeutic methods were mostly adopted and that special efforts were made in this regard. On the other hand, it was observed that improper attitudes and behaviors such as restricting the communication, blaming and using the language of conflict were exhibited, although they were not frequent. In cases where nurses had difficulty in coping with the problems, it was observed that they tended towards non-therapeutic approaches since they felt helpless. In this context, it is observed that educational activities are needed so that nurses' coping skills in crisis situations can be improved and they have more information about professional approaches^{24,33}. A supportive setting established with therapeutic interventions will make significant contributions for patients and their relatives to gain awareness, to reduce anxiety, and to encourage communication^{8,35}.

When nurses were asked about solution suggestions to reduce/eliminate communication difficulties, they made suggestions on the necessity of strengthening the therapeutic care setting and the nurses in parallel with the difficulties experienced and coping behaviors. In line with these results, it can be

said that the nurses who participated in the study had a high level of awareness. However, it was determined that they had difficulties in implementing their suggestions and finding solutions. Strengthening the therapeutic care setting is an issue that requires multifaceted attempts. Therefore, it is a long-term working area that requires nurses to collaborate with the patients and their relatives, other members of the healthcare team, managers and other stakeholders^{31,34}. Good communication and teamwork with the patients, their relatives and the team, supporting the patient and their families, and education are essential requirements for qualified nursing care³⁶. A multi-stage approach involving primarily nurses at the clinical level and then other stakeholders can be suggested for the solution of problems.

Study Limitations

This study was conducted through purposive sampling, by including the nurses who had experience in communication difficulties with patients having brain tumors. This non-probabilistic sampling method is limited to the generalizability of study results. This study can create a data source for examining the phenomenon with quantitative research designs in larger different sample groups using probabilistic sampling methods.

CONCLUSION

Communication between nurses and patients and between nurses and other team members is an area that needs more focus as an issue of patient safety. In line with the communication difficulties, coping methods and solution suggestions defined in this study, the importance of establishing the therapeutic care setting, eliminating the lack of information given to patients/their relatives, and adopting an individualized care approach with the participation of individuals and their families in care processes was revealed for the management of possible/existing communication difficulties. Nevertheless, it may be suggested that nurses should communicate effectively with other healthcare team members, collaboration should be strengthened, institutional factors causing communication difficulties should be identified, and attempts should be made for solutions.

Ethics

Ethics Committee Approval: Ethical approval from İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (decision number: 45977, date: 05/02/2016).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., G.Ö.A., H.K., R.A., Design: A.Ö., H.K., R.A., Data Collection or Processing: A.Ö., G.Ö.A., K.Ş., Analysis or Interpretation: A.Ö., H.K., R.A., Literature Search: A.Ö., G.Ö.A., K.Ş., Writing: A.Ö., G.Ö.A., H.K.

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The Protective Effects of Diclofenac Sodium and Montelukast Sodium on Acute Inflammation in Traumatic Spinal Cord Injury: An Experimental Study in Rats

Diklofenak Sodyum ve Montelukast Sodyumun Travmatik Omurilik Yaralanmalarında Akut Enflamasyon Üzerindeki Koruyucu Etkileri: Sıçanlarda Deneysel Bir Çalışma

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ABSTRACT

Aim: The aim of this study was to investigate the protective effects of diclofenac sodium (DF) and montelukast sodium (ML) on acute inflammation in traumatic spinal cord injury (T-SCI).

Materials and Methods: Forty Sprague-Dawley rats were randomly divided into five groups. While no intervention was made in the control group, spinal cord injury was applied to the trauma group. DF, ML and DF+ML were administered intraperitoneally to the remaining three groups after trauma. After rats were sacrificed, tissue samples containing both spinal cord and dura were subjected to histopathological examination and scored for edema, necrosis, inflammatory cells, apoptosis, neuron damage, and bleeding.

Results: There was a significant difference in the histopathological changes between the control and trauma groups ($p<0.05$). Histopathological scores of the trauma group and trauma+drug groups were similar ($p>0.05$). In the comparison of the control group and the other groups, no significant difference in edema was found in the tDF group ($p=0.059$). When the inflammatory cells were examined, it was seen that the cell amount was the least in the tDF group ($p=0.068$). It was observed that necrosis ($p=0.1$), apoptosis ($p=0.061$) and neural damage status ($p=0.139$) were the least in the tDF+ML combined group. There was no significant difference between the groups in terms of the amount of bleeding ($p>0.05$).

Conclusion: While the use of DF alone reduced the number of edema and inflammatory cells, the combined use of DF+ML reduced the development of necrosis, apoptosis and neural damage in T-SCI.

Keywords: Diclofenac sodium, inflammation, montelukast sodium, spinal cord injury, trauma

ÖZ

Amaç: Bu çalışmanın amacı travmatik omurilik yaralanmasında (T-SCI) diklofenak sodyum (DF) ve montelukast sodyumun (ML) akut enflamasyon üzerindeki koruyucu etkilerini araştırmaktır.

Gereç ve Yöntem: Kırk Sprague-Dawley sıçanı rastgele beş gruba ayrıldı. Kontrol grubuna herhangi bir müdahale yapılmazken, travma grubuna SCI uygulandı. Kalan üç gruba travma sonrası diklofenak sodyum (tDF), ML (tML) ve tDF+ML intraperitoneal yolla uygulandı. Sıçanlar sakrifiye edildikten sonra hem omurilik hem de dura içeren doku örnekleri histopatolojik incelemeye tabi tutuldu ve ödem, nekroz, enflamatuvar hücreler, apoptoz, nöron hasarı ve kanama açısından skorlandı.

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Bulgular: Kontrol ve travma grupları arasındaki histopatolojik değişikliklerde gruplar arasında anlamlı fark bulundu ($p<0,05$). Travma grubu ve travma+ilaç gruplarının histopatolojik skorları benzerdi ($p>0,05$). Kontrol grubu ile gruplar arasında ödem farkı olmayan grubun tDF grubu olduğu görüldü ($p=0,059$). Enflamatuvar hücreler incelendiğinde hücre miktarının en az tDF grubunda olduğu izlendi ($p=0,068$). Nekroz ($p=0,1$), apoptoz ($p=0,061$) ve nöral hasar durumunun ($p=0,139$) tDF+ML kombine grubunda en az olduğu görüldü. Kanama miktarı açısından gruplar arasında anlamlı bir fark yoktu ($p>0,05$).

Sonuç: DF'nin tek başına kullanımı ödem ve enflamatuvar hücre sayısını azaltırken, DF+ML'nin birlikte kullanımının T-SCI'da nekroz, apoptoz ve nöral hasar gelişimini azalttığı saptandı.

Anahtar Kelimeler: Diklofenak sodyum, enflamasyon, montelukast sodyum, omurilik yaralanması, travma

INTRODUCTION

Spinal cord injury (SCI) is a condition that can have temporary or permanent impact on spinal cord functions and that has physically, psychologically and socially devastating outcomes¹. The incidence of SCI varies among geographical regions and over time. Annual incidence rate is reported to be 10.4-83 people per million².

Despite all therapeutic options, traumatic spinal cord injury (T-SCI)-related morbidity and mortality remain high³. Initially, primary injury occurs with the involvement of the spinal cord and surrounding tissues due to trauma-related mechanical reasons. Thereafter, secondary injury occurs by various mechanisms. Progressive edema, increasing ischemia and triggered pro-apoptotic pathways lead to additional tissue injury and the process results in cell death⁴. Primary injury usually cannot be prevented and its severity cannot be changed as it occurs due to unexpected reasons during this process. Thus, preventing or reducing and ameliorating secondary injury has been the main goal of the treatment. Nevertheless, there is yet no definite approach for the prevention or management of secondary injury, and numerous agents are under investigation⁵. Non-steroidal anti-inflammatory drugs (NSAIDs) as well are among the pharmacological agents used in the experimental and clinical studies.

Inflammation is a defense mechanism against injury. However, inflammatory processes may have harmful effects as well as benefits depending on various factors and time⁶. Anti-inflammatory drugs are used to reduce/ameliorate secondary injury by means of preventing/reducing inflammation. Montelukast sodium (ML) is a leukotriene receptor antagonist that reduces its effects by binding to cysteinyl leukotriene receptors to which leukotrienes, one of the arachidonic acid metabolites released from mast cells, eosinophils and other inflammatory cells that play a role in inflammation⁷. Diclofenac sodium (DF), on the other hand, has an anti-inflammatory effect by inhibiting cyclooxygenase 1 and 2 (COX-2) enzymes involved in arachidonic acid metabolism, preventing the synthesis of inflammatory mediators⁸.

The present study aimed to investigate whether the inflammatory agents, DF and/or ML had protective effects

on acute inflammation in T-SCI cases. For this purpose, an experimental rat model of T-SCI was created and histopathological examination was performed to investigate the effect of drugs on trauma-related injury.

MATERIALS AND METHODS

In the present study, 40 male Sprague-Dawley rats aged between 10 and 12 weeks and weighing 230-280 gr were used. This study was approved by the Local Ethics Committee for Animal Experiments at the meeting of the University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital (decision number: 2017-05/05, date: 01.11.2017). As anti-inflammatory drugs, DF (Voltaren, Novartis, İstanbul, Turkey) and ML (Singulair, Merck Sharp Dohme, İstanbul, Turkey) were used.

The rats were divided into 5 groups, each comprising 8 rats, as follows:

1. The control group (C): no SCI and no medication
2. The trauma group (T): only spinal cord injury, no medications.
3. The trauma+DF group (tDF): diclofenac administration after spinal cord injury.
4. The trauma+ML group (tML): montelukast administration after spinal cord injury.
5. The trauma+DF+ML group (tDF+ML): diclofenac+montelukast administration after spinal cord injury.

All the rats were kept in rooms provided with adequate air circulation and ambient temperature without food or water restriction. Following spinal cord injury, the subjects were placed in an appropriate environment for the maintenance of care, their daily dressing was done, and the subjects in the treatment groups received relevant medications.

Surgical Procedure

SCI was created in all rats excluding those in the control group. Prior to the surgical procedure, ketamine 60 mg/kg (Ketalar, Parke-Davis, Eczacıbaşı, İstanbul, Turkey) and Xylazine 10 mg/kg (Rompun, Bayer Pharmaceuticals, İstanbul, Turkey) were administered for general anesthesia. Surgical procedures

were performed on rats fixed in prone position onto the experimental boards. The surgical area was shaved, and regional antisepsis was provided using povidone iodine solution (Povidon 10% polyvinylpyrrolidone-iodine complex, Saba İlaç, İstanbul, Turkey). After covering with sterile drapes, cutaneous and subcutaneous incisions were made at the level of T9-T12 vertebrae. Subperiosteal stripping of the paravertebral muscles was performed. Following T9-T10-T11 laminectomy and flavectomy, the dura was exposed. Extradural SCI was created by one minute compression of the spinal cord using Yaşargil Aneurysm Clip.

Drug Administration

Diclofenac sodium: The subjects in the relevant groups were administered 10 mg/kg DF twice a day by intraperitoneal route for 72 hours after spinal cord injury.

Montelukast sodium: The subjects in the relevant groups were administered 10 mg/kg ML twice a day by intraperitoneal route for 72 hours after spinal cord injury.

Follow-Up

After 72-hours of medical treatment and follow-up period, the subjects were sacrificed using 100 mg/kg pentothal sodium (Pental Sodyum, Ulagay İlaç, İstanbul, Turkey). The operation site was opened under sterile conditions and the lesion area was exposed. The spinal cord, dura and the surrounding tissues including 5 mm of intact tissue from both proximal and distal segments were excised together. These tissue samples were fixed in 10% formalin solution and then were transferred to the laboratory for histopathological examination. During follow-up period, a total of two subjects, one from the trauma group and one from the trauma+DF group, died.

Histopathological Examination

The sections obtained from the tissue samples were stained with hematoxylin-eosin, and were examined under light microscope for the presence of edema, necrosis, inflammatory cells, apoptosis, neuron injury, and bleeding, and each finding was scored with the grading system which was summarized in Table 1. The histopathological examination findings can be seen in Figure 1.

Statistical Analysis

The Number Cruncher Statistical Software 2007 (NCSS, LLC, Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistics were expressed as numbers and percentages for categorical variables and as median, 25th percentile, and 75th percentile for numerical variables. In multiple group comparisons with non-normal distribution, the Kruskal-Wallis test was used, whereas pairwise comparisons were performed

using the Mann-Whitney U test with Bonferroni correction. The level of statistical significance was considered to be $p < 0.05$.

RESULTS

The histopathological scores and statistical differences between the control group and other groups are summarized in Table 2. It was observed that the parameters between the control group and the trauma group were significantly different ($p < 0.05$). Histopathological scores of the trauma group and trauma+drug groups were similar ($p > 0.05$). The edema levels among the groups were examined and it was seen that the group with no difference was the tDF group compared to the control group ($p = 0.059$) and the groups with a significant difference were the tDF+ML group ($p = 0.034$) and the tML group ($p = 0.007$), respectively. It was observed that the least edema was in the tDF group. In the evaluation of necrosis, the group with the least necrosis was tDF+ML ($p = 0.1$), while the groups with more necrosis were tDF ($p = 0.017$) and tML ($p = 0.008$). Considering the number of inflammatory cells, the lowest number of cells was observed in the tDF group ($p = 0.068$), while more cells were observed in the tDF+ML group ($p = 0.035$) and in the tML group ($p = 0.002$), respectively. While

Table 1. Grading system of histopathological changes

Grade	Histopathological changes
0	No change
1	Changes are present in less than 25% of the area
2	Changes are present in 25-50% of the area
3	Changes are present in 51-75% of the area
4	Changes are present in 76-99% of the area
5	Changes are present in the entire area

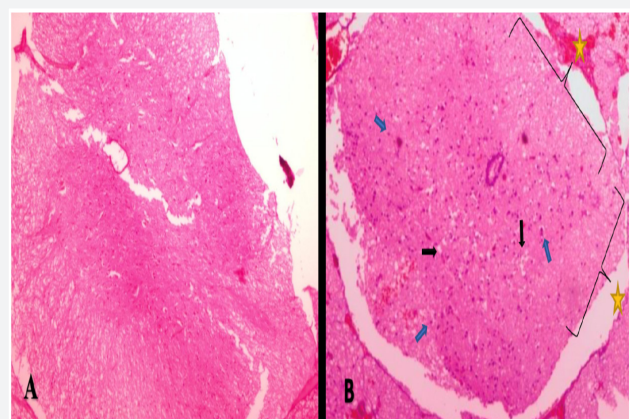


Figure 1. A) Histopathological section of the control group. B) Histopathological section of the trauma group. Numerous inflammatory cell images (blue arrows), areas of necrosis (black arrows) and prominent peripheral edema areas (areas marked with asterisks)

Table 2. Histopathological scores and statistical differences between the control group and other groups

	Edema		Necrosis		Inflammatory cell		Apoptosis		Neuron injury		Bleeding	
	Median	p	Median	p	Median	p	Median	p	Median	p	Median	p
Control	0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)	
Trauma	5 (4-5)	0.001	5 (4-5)	0.001	5 (3-5)	0.001	5 (4-5)	0.001	5 (5-5)	0.001	5 (3-5)	0.001
tDF	2 (2-3)	0.59	4 (3-4)	0.017	3 (2-3)	0.068	3 (2-4)	0.039	3 (3-4)	0.011	3 (3-3)	0.031
tML	3 (2-4)	0.007	4 (3-4)	0.008	3 (3-4)	0.002	3 (3-4)	0.004	4 (3-4)	0.005	3 (2-4)	0.014
tDF+ML	2 (2-4)	0.034	2 (2-4)	0.1	3 (2-3)	0.035	3 (2-3)	0.061	3 (2-3)	0.139	3 (2-4)	0.014

tDF: Trauma+diclofenac sodium, tML: Trauma+montelukast, tDF+ML: Trauma+diclofenac sodium+montelukast

the group with the least apoptosis was tDF+ML ($p=0.061$), it was found to be significantly higher in the tDF group ($p=0.039$) and tML group ($p=0.004$), respectively. While neuronal injury was seen at least in the tDF+ML group ($p=0.139$), significant neural damage was observed in the tDF group ($p=0.011$) and tML group ($p=0.005$), respectively. Considering the amount of bleeding in the preparations, it was observed that there was significant bleeding in all groups compared to the control group ($p<0.05$).

DISCUSSION

T-SCIs are clinical conditions that may lead to devastating physical, psychological and social consequences in the lives of patients. However, a definitive treatment method has not been developed despite all the researches and treatment modalities applied today¹. The severity of primary injury is the most critical factor in determining the prognosis of T-SCI. Nevertheless, the mechanisms leading to secondary injury may intensify the injury or may affect healing processes and thus, may affect overall morbidity and mortality.

Inflammation has a critical role in secondary damage. The aim of inflammation is to stabilize and limit the existing damage, and to fulfill the necessary conditions for the repair of the organism, to clean the cell residues and to remove harmful substances in the environment. In case of high severity, neuronal cell damage may increase with the increase of damage, and as a result, functional results may worsen^{9,10}. The mechanisms of secondary injury are complex and include various conditions such as neurogenic shock, bleeding, ischemia-reperfusion, excitotoxicity, calcium-mediated processes, fluid-electrolyte imbalance, immunological processes, apoptosis, and mitochondrial dysfunction¹¹. So far, various medical agents have been investigated for the treatment of SCI. These agents include corticosteroids, vasopressors, minocycline, magnesium, riluzole, glyburide (glibenclamide), thyrotropin-releasing hormone, opioid receptor antagonists (naloxone), granulocyte colony stimulating factor, cethrin, gangliosides, antioxidants, calcium channel blockers, sodium channel blockers, and many others^{12,13}. Corticosteroids are being used for a long time in many

experimental and clinical trials due to their anti-inflammatory, edema-resolving and antioxidant characteristics. However, it is currently accepted that corticosteroids have no effect when compared to placebo at 6-12 months of follow-up and therefore have no long-term benefits¹⁴.

Due to the strong anti-inflammatory effects of NSAIDs, it is expected that they may have anti-inflammatory effects in secondary damage. In experimental studies, inhibition of the RhoA pathway and neuroprotective effect by reducing apoptosis and providing histological improvement bring these drugs to a promising position in terms of treatment¹⁵. In our study, when the edema level among the groups was examined, it was seen that the group that did not differ from the control group was the tDF group. There was no significant difference in the ML group in terms of edema. In addition, when the tDF+tML group and other drug groups were compared, it was found that combined drug administration reduced the anti-edema effect compared to single applications. In the study of Saiwai et al.¹⁶, the importance of leukotrienes in the injury mechanisms after SCI was emphasized. In the study conducted by Cavus et al.¹⁷, the effects were compared with montelukast and methylprednisolone and it was reported to be neuroprotective. Genovese et al.¹⁸ compared the effects of montelukast and zilueton and found the anti-edema effects to be significant.

Inflammation is the basic defense mechanism of the organism and begins to appear in the trauma area in the 3rd post-traumatic hour and can remain at the maximum level until the 3rd day¹⁹. Schwartz²⁰ reported that the presence of neutrophils was necessary for repair after axonal damage and that T lymphocytes in the environment were necessary for defensive and repair events. Schwab et al.²¹ stated that the amount of LTC₄ and TXA₂, which are arachidonic acid metabolites in CSF, increased 5-9 times higher than normal after the injury. In our study, when the number of inflammatory cells in the groups was compared, it was found that the number of cells was the lowest in the tDF group. No significant difference was found in the other groups. Hains et al.²² reported that COX-2 inhibitors improved histological and motor function results.

In the literature, studies in which indomethacin and ketorolac were applied intrathecally have been reported to have a protective effects^{23,24}. Genovese et al.¹⁸ also showed that zileuton and montelukast sodium, which are 5-lipoxygenase inhibitors, decreased the number of inflammatory cells and myeloperoxidase activity, which increased in the 24 hours after trauma.

As a result of the comparisons between the groups, it was seen that necrosis, apoptosis and neural injury were the least in the group, in which tDF+ML was used in combination, compared to the other groups. It has been shown that caspas-8 and 9 are activated in the lesion center at the 6th hour after trauma and this activity lasts for 7 days²⁵. Inflammatory cytokines, especially TNF- α released from neurons, activate the RhoA pathway and cause apoptosis²⁴. Mills et al.²⁶ showed that activated Rho pathway induced Bcl-2 dependent apoptosis. Xing et al.²⁷ stated that the inhibition of RhoA in rats, which they applied NSAID treatment for 5 post-traumatic days, especially protected oligodendrocytes from apoptosis, and increased axonal myelination in the rostral and caudal of the lesion. In the experimental study on rats, Wang et al.²⁸ reported that the treatment of ibuprofen given at a dose of 60-70 mg/kg for 1-28 days had a protective effect on the rostral axons of the spinal cord, but this effect was not observed in the caudal fibers. As a result, they stated that ibuprofen could be a potential agent. Sharp et al.²⁹ reported that 60 mg/kg ibuprofen treatment for 42 days after trauma resulted in improvement in Basso-Beattie-Bresnahan score and protection in motor functions in rats as a result of treatment.

Post-traumatic bleeding is a pathology that begins to occur after primary injury and continues with secondary injury. In their study, Noble and Wrathall³⁰ stated that the localization of bleeding after SCI was related to the severity and direction of the blow that caused the primary injury, and they reported that bleeding localizations could be seen simultaneously in the rostral and caudal regions of the spinal cord and in more than one region. Erşahin et al.³¹ reported that ML reduced bleeding in the spinal cord white matter. Saiwai et al.¹⁶ reported that neutrophils that migrated to the environment at the 12th hour after trauma increased the bleeding status and this situation decreased due to the decreased cell migration after the use of ONO-4057, which is an LTB₄ antagonist. In our study, we detected that there was no significant difference between the groups in terms of the amount of bleeding.

Study Limitations

The most important limitation of our study is that it is not supported by functional recovery and biochemical parameters such as apoptosis and inflammation markers, as well as investigating the pathological changes.

CONCLUSION

In our study, it was determined that the application of DF alone in traumatic SCI had a reducing effect in the development of edema and the number of inflammatory cells, while the application of DF+ML had a reducing effect on the development of necrosis, apoptosis, and neural damage.

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Ethics

Ethics Committee Approval: The study were approved by the Local Ethics Committee for Animal Experiments of University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital (decision number: 2017-05/05, date: 01.11.2017).

Informed Consent: Animal experiments.

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Authorship Contributions

Surgical and Medical Practices: T.E., D.C., F.V.A., Concept: T.E., B.E., Design: T.E., M.İ., F.V.A., Data Collection or Processing: T.E., D.C., F.V.A., Analysis or Interpretation: T.E., F.V.A., T.T., T.Ç., Literature Search: T.E., M.İ., B.E., Writing: T.E., M.İ., B.E., T.T., T.Ç.

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Demographic Examination of Patients with Oncologic Diagnosis Admitted to the Emergency Department

Acil Servise Başvuran Onkolojik Tanılı Hastaların Demografik İncelenmesi

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ABSTRACT

Aim: Prolongation in the life span of cancer patients has resulted in increased number of cancer patients all over the world. However, this change is increasing the number of oncological patients admitted to the emergency departments every day. This study aimed to determine the reasons for admission to the emergency department (ED) for cancer patients and to examine the factors affecting the prognosis demographically.

Materials and Methods: Patients aged 18 years or older with clinical/pathological oncologic diagnoses, who applied to Tekirdağ Namık Kemal University Hospital Emergency Department between March 1st 2018 and August 31st 2018, were included in the study. The study was prospective and ethics committee approval was obtained prior to the study.

Results: Totally 265 patients with pathology reports for confirmed oncology diagnosis were included in the study. The most common reason was "pain" with a rate of 13.6% (n=36). Gastrointestinal system symptoms and respiratory system symptoms were the most common reasons for hospitalization in clinics and intensive care units and patients who had these symptoms died with the rates of 6.8% (n=18) and 33.3% (n=30), respectively, in clinics.

Conclusion: The most common reasons for ED visits by cancer patients are pain, nausea and vomiting, abdominal pain, and shortness of breath. Oncology patients admitted to the ED have higher needs for laboratory tests, radiological imaging and consultation, and time to be followed in the emergency services.

Keywords: Oncology, emergency, medicine

ÖZ

Amaç: Hasta bakımındaki iyileşmeler sayesinde kanser hastalarının yaşam süresindeki uzamalar tüm dünyada kanserli hasta sayısının giderek artmasına neden olmaktadır. Bununla beraber acil servise başvuran onkolojik hastaların sayısı da gün geçtikçe artmaktadır. Bu çalışma ile kanserli hastaların acil servise başvuru nedenleri ve prognozu etkileyen faktörleri demografik olarak incelenmiştir.

Gereç ve Yöntem: Çalışmaya Tekirdağ Namık Kemal Üniversitesi Hastanesi Acil Servisi'ne 1 Mart 2018 tarihi ile 31 Ağustos 2018 tarihi arasında başvuran ve klinik/patolojik/onkolojik tanısı olan 18 yaş ve üzeri hastalar dahil edildi. Çalışma prospektif olup, başlamadan önce etik kurul onayı alındı.

Bulgular: Çalışmaya onkoloji tanısı patoloji raporları ile kesinleşmiş 265 hasta dahil edildi. Olguların yaş ortalaması 60±12 yıl olup, kadınlardaki yaş ortalamasının 58±13 yıl olduğu görüldü. En sık başvuru şikayeti %13,6 (n=36) ile "ağrı" oldu. Kliniklere ve yoğun bakım ünitelerine en sık yatış nedeninin %6,8 (n=18) ile gastrointestinal sistem patolojileri ve respiratuvar patolojiler olduğu görüldü. Yatışı yapılan 90 hastadan %63,3'ünün (n=57) hastaneden taburcu edildiği ve %33,3 (n=30) hastanın ise yatırıldığı kliniklerde vefat ettiği saptandı.

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Sonuç: Onkolojik hasta gruplarının yaş ortalaması yüksek olduğu için morbiditesi ve mortalitesi diğer hasta gruplarına göre daha yüksektir. Bu sebeple bu hasta grupları acil servise diğer hasta gruplarına göre farklı şikayetlerle gelebilmektedirler. Onkolojik hastaların tetkik ve tedavilerinin daha dikkatli düzenlenmesi gerekmektedir.

Anahtar Kelimeler: Onkoloji, acil, tıp

INTRODUCTION

The number of cancer patients admitted to the emergency departments is increasing every day. There are several possible reasons for this increase. The improvement in living standards has resulted in an increase in the population aged over 65 years in parallel with an increase in the incidence of age-dependent oncological diseases. With the improvement in the quality of life, there has also been an increase in the prevalence of cancer in parallel with the increased population aged 60 years and over¹. However, with the improvements in patient care, the prolongation in the survival of cancer patients results in the increase in the number of cancer patients relatively in the society¹.

According to the data of the World Health Organization (WHO), cancers are the second most common reason for deaths worldwide and they were thought to be responsible for 9.6 million deaths in 2018². Globally, cancer types are the first or second common cause of premature deaths (between the ages of 30 and 69 years) in 134 out of 183 countries². The economic burden of cancer patients for countries is gradually increasing, and the total annual economic cost of cancer patients in 2010 was estimated to be 1.16 trillion USD².

Cancer is a chronic disease and cancer patients can apply to emergency services with a wide variety of complaints. These complaints can roughly be classified as conditions directly caused by the existing cancer (pain, compression, bleeding), conditions that develop due to chemotherapy treatment (tumor lysis, febrile neutropenia), and conditions indirectly caused by cancer (infectious, metabolic)³. Patients may apply to emergency services with only one or a combination of several of these above conditions. Many of these disease conditions are life threatening and require immediate diagnosis and treatment. Early diagnosis and appropriate treatment are effective in improving the comfort care of the patient⁴. The first application points of these patient groups in hospitals are frequently the emergency services. This situation increases the number of emergency service applications and intensities.

In this study, it was aimed to investigate the common reasons for admission, problems that were encountered, and demographic data of oncology patients admitted to an emergency department. Recognition of these situations will contribute to the emergency service workers' realization of the potential risks in cancer patient groups and improve the regulation of the patience approach policies.

MATERIALS AND METHODS

Before the study, the approval from Namık Kemal University Non-Invasive Clinical Research Ethics Committee was obtained (approval number: 2018/19/02/04, date: 19.02.2018).

Studied Population

Patients with clinical/pathological oncological diagnosis, aged 18 years and over, who applied to Tekirdağ Namık Kemal University Emergency Service between March 1st 2018 and August 31st 2018 and who signed the "Volunteer Consent form" were included in the study. Patients with a clinical/pathological oncological diagnosis, whose complaint at admission to the emergency service was not related to oncological disease (such as having breast carcinoma but brought to the emergency room due to a traffic accident or having lung cancer but applying due to extremity trauma etc.), were excluded from the study.

Study Protocol

The data of the patients who met the study inclusion criteria and who signed the "Volunteer Consent form" were recorded in the patient data record form. The observation and inspection data, duration of stay in the emergency service and emergency/clinical outcomes of the patients whose treatments were completed in the emergency department were analyzed on the "Hospital Information Management System" and recorded in the study form.

Clinical Outcomes of the Study

The primary endpoint of our study was to define the reasons for admission to the emergency department for patients with oncological diagnosis, and the secondary endpoint was to determine the emergency room outcomes of the patients.

Statistical Analysis

The data obtained from the study were recorded in the standard software of "Statistical Package for Social Sciences for Windows 20.0" to conduct statistical analysis. The t-test was used for the comparison of the means, and the chi-square test was used to compare the variables determined by counting.

RESULTS

Totally 265 patients with oncology diagnosis confirmed by pathology reports were included in the study. The youngest and the oldest patients were 19 and 84 years old, respectively.

52.1% (n=138) of the patients were male. The mean age of the cases was 60 ± 12 years, and the average age in women was 58 ± 13 years. It was found that 87.9% (n=233) of the patients were self-applied to the emergency service and 12.1% (n=32) by 112 emergency ambulance (Table 1).

The most prevalent complaints of patients were gastrointestinal system (GIS) complaints with a rate of 40.8% (n=108), followed by respiratory system complaints with a rate of 15.8% (n=42). The most prevalent symptom was "pain" with the rate of 13.6% (n=36) (Table 2).

When the cancer classifications of the patients were examined, it was determined that the most common types were GIS malignancies with the rate of 31.7% (n=84), followed by respiratory system and intrathoracic organ neoplasms with the rate of 27.5% (n=73). It was found that 61.5% (n=163) of the patients were metastatic and 85.7% (n=227) of the patients were under medical follow-up by the Medical Oncology department. It was determined that 87.2% (n=231) and 30.6% (n=81) of the studied patients were previously given chemotherapy and radiotherapy, respectively. It was determined that 46.4% (n=123) of the patients undergone oncological surgery and 74.7% (n=198) had no known family history at 1st and 2nd degree relatives (Table 3).

When the conditions of the patients in the emergency service were examined, it was determined that laboratory examination was requested at the time of admission to the emergency department from 91.3% (n=242) of the 265 patients included

in the study. When the outcomes of the patients were monitored in the emergency department, it was determined that 49.8% (n=132) of patients were consulted to the relevant units, 62.6% (n=166) were discharged from the emergency department and 34% (n=90) were admitted to the service and intensive care units. It was observed that 27.5% (n=73) of the patients were followed up in the emergency department for four hours or more (Table 4).

Among the patients who were admitted to clinics and intensive care units, the most common reasons for hospitalization were GIS pathologies and respiratory pathologies with 6.8% (n=18), followed by hematological problems with 5.7% (n=15). The most common reason for hospitalization was neutropenic fever in 9 patients (3.4%), followed by pain palliation in 7 patients (2.6%). It was determined that 63.3% (n=57) of the 90 hospitalized patients were discharged from the hospital and 33.3% (n=30) of the patients died in the clinics where they were hospitalized. Patients who died (23.3%, n=7) were found to be hospitalized for palliative purposes. Of the 30 patients who died, 40% (n=12) and 33.3% (n=10) were previously diagnosed with "respiratory and intrathoracic neoplasm" and "GIS malignancy", respectively. It was observed that 25% (n=8) and 34.3% (n=11) of 32 patients which were brought to the emergency room by 112 ambulance were admitted to intensive care units and to service floors, respectively.

DISCUSSION

The yearly increases in oncology cases around the world has a reflection in emergency room admission numbers, which is becoming a serious problem for the management of emergency services that are currently very busy. According to WHO data, it is estimated that the number of active cancer patients in 2020 was over 19 million and 9.9 million (17.8%) of 55.4 million deaths in the world in 2019 were caused by cancer. Moreover, this number is expected to be over 16 million in 2040⁵. Of more than 10 million newly diagnosed cancer patients within a year, 53% are men and 47% are women⁴. Kerrouault et al.⁶ found that 65% of the patients with an oncological diagnosis, who applied to the emergency department, were male and the average age was 62 years. Kocak et al.⁴ found in their study that 58% of the patients were male. In our study, we found

Table 1. Demographic characteristics of the patients

Demographic data	Result
Gender	
Male	52.1% (n=138)
Female	47.9 % (n=127)
Type of application to service	
112 emergency ambulance	12.1% (n=32)
Outpatient and self-referred	87.9% (n=233)
Average age	
Male	60 ± 12 (19-84) years old
Female	58 ± 13 years old

Table 2. Complaints and experienced symptoms of patients

Systemic	%	n	Symptoms	%	n
GIS	40.8	108	Pain (muscle-joint, tumor)	13.6	36
General symptoms and signs*	35.5	94	Nausea and vomiting	13.2	35
Respiratory symptoms	15.8	42	Abdominal pain	12.8	34
Neurological symptoms	6.4	17	Shortness of breath	12.5	33

*Complaints such as pain, fever, gingival bleeding, epistaxis, hematuria and others were recorded as general symptoms and signs.

GIS: Gastrointestinal system

Table 3. Oncological characteristics of patients		
Cancer classification	%	n
GIS malignancy	31.7	84
Respiratory and intrathoracic neoplasm of organs	27.5	73
Neoplasm of organs	11.3	30
Hematological malignancy	10.2	27
Metastasis		
Present	61.5	163
Absent	38.5	102
Host clinic		
Medical oncology	85.7	227
Hematology	10.2	27
General surgery	1.9	5
Chemotherapy history		
Present	87.2	231
Absent	12.8	34
Radiotherapy history		
Present	30.6	81
Absent	69.4	184
Surgery history		
Present	46.4	123
Absent	53.6	142
Family history		
Present	25.3	67
At 1 st degree relatives	23.0	61
At 2 nd degree relatives	2.3	6
Absent	74.7	198
GIS: Gastrointestinal system		

that 52.1% of the patients were male, 47.9% were female, the average age was 60 years, and we found that these findings were consistent with the literature.

Siegel and Bigeraw⁷ found that the importance of palliative care in emergency services was increasing, symptoms related to pain, nausea and shortness of breath were common especially at oncology patients in the last period of their life, and these type of patients applied to the emergency services for these symptoms⁷. In our study, we found that the most common symptom was "pain" (26.4%, n=70), followed by "nausea and vomiting" (13.2%, n=35) and "shortness of breath" (12.5%, n=33). Palliation of pain in oncology patients is difficult with non-opioid drugs due to its physiopathology and needs for opioids are frequent, which can be considered as another factor that increase the frequency of hospital admissions.

The most common type of cancer encountered in the emergency department was reported to be lung cancer in

Table 4. Features of emergency service applications		
	%	n
Laboratory examination		
Present	91.3	242
Absent	8.7	23
Radiological examination		
Present	66.8	177
Absent	33.2	88
Consultation prompt		
Present	49.8	132
Absent	50.2	133
Emergency service outcome		
Discharge from the emergency service	62.6	166
Admission to the service	27.2	72
Admission to the intensive care unit	6.8	18
Voluntarily leave of the emergency service	2.6	7
Referral to another hospital	0.8	2
Duration of follow-up in emergency department		
0-1 hours	4.9	13
1-2 hours	25.3	67
2-3 hours	21.1	56
3-4 hours	21.1	56
>4 hours	27.5	73

studies of Swenson et al.¹ (16%) and Yaylacı et al.⁸. In their study, Işıkber⁹ reported that the most common type of cancer was GIS tumors in the applications followed by lung cancer in the second order. In our study, we found that GIS malignancies were ranked first with a rate of 31.7% (n=84), followed by "respiratory system and intrathoracic organ neoplasms" with a rate of 27.5% (n=73).

In their study, Yaylacı et al.⁸ found that the most common complaint was pain and the second most common complaint was shortness of breath. In our study, we found that the most common complaint was pain, followed by nausea and vomiting, and then by dyspnea.

Işıkber⁹ reported in their study that 36% of the cases were metastatic at admission stage. Çoban³ reported in their study that 72% of patients were metastatic at the time of admission. In our study, we found that 61% of the cases were metastatic at the time of admission, which we associated this high value with the status of tertiary healthcare institution, admitting advanced and complicated cases.

Barrett and Hamilton¹⁰ reported in their study that 23% of lung cancer cases were hospitalized urgently. In our study, we found that 28 (38.3%) of 73 patients diagnosed with "neoplasm of respiratory and intrathoracic organs" were hospitalized in service and intensive care units. We associated

this high rate of hospitalization with the approach that the respiratory problems were the leading causes of mortality and morbidity in patients and therefore physicians had a lower hospitalization threshold for hospitalization.

Işıkber⁹ examined the emergency service outcomes of the patients and reported in their study that 70% of the patients were discharged from the emergency service and 23% were hospitalized. In our study, we observed that 62% of the patients were discharged from the emergency department, and 34% were admitted to the service and intensive care units. In other studies, hospitalization rates in the general patient population in tertiary emergency services were found to be reported between 12% and 13%^{11,12}. This shows that the hospitalization rate of oncology patients is high, compared to all admissions, due to the difficulty of pain palliation in cancer patients and the difficulty of home care for cancer patients.

Study Limitations

The limitation of this study should be considered when interpreting our results. First, the present study is a prospective study with relatively small sample size. Second, limited parameters were examined in a limited time period in this study. Therefore, our results should be verified in multi-center prospective longitudinal studies with larger sample size.

CONCLUSION

For many cancer patients, emergency services are the entrance point to the hospitals. Frequent applications of these patients increase the intensity in the emergency services. Morbidity and mortality of these patient groups are higher compared to other patient groups. Due to this reason, oncological patients should be investigated more detailed in emergency departments. Separating oncological patients from other groups of patients in the emergency rooms in a section may be useful to achieve this target. Multi-center studies with more detailed data on wider populations will be more beneficial and guiding.

Ethics

Ethics Committee Approval: This study was approved by the Tekirdağ Namık Kemal University Non-Invasive Clinical Research Ethics Committee was obtained (approval number: 2018/19/02/04, date: 19.02.2018).

Informed Consent: Informed consent was obtained from all subjects involved in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.N.E., R.M.Y., Concept: H.Ş., S.B., Design: H.Ş., S.B., M.Ç., Data Collection or Processing: S.B., M.N.E., N.B., S.Ö., Analysis or Interpretation: S.B., N.B., M.Ç., S.Ö., R.M.Y., Literature Search: S.Ö., R.M.Y., Writing: H.Ş., R.M.Y.

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The Factors Affecting Recoarctation Development After Surgical Correction in Patients with Aortic Coarctation

Aort Koarktasyonu Tanısıyla Cerrahi Düzeltme Uygulanan Hastalarda Rekoarktasyon Gelişimi Üzerine Etki Eden Faktörler

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ABSTRACT

Aim: In this study, the factors affecting the development of recoarctation in patients who had been operated for aortic coarctation (AC) were investigated. It was aimed to contribute to the reduction of recoarctation rates in the light of the results obtained.

Materials and Methods: In this retrospective study, 217 patients out of 358 patients, who underwent surgical correction for the diagnosis of AC at Hacettepe University Faculty of Medicine, Department of Cardiovascular Surgery between 1977 and 2010, who were followed up regularly, and whose data could be reached, were included. Age, body weight and results of surgical correction techniques used during surgical correction were compared in cases having recoarctation. Data obtained were evaluated statistically. Descriptive statistics for categorical variables were stated as numbers (n) and percentages (%). The results were presented in mean±standard deviation and/or percentage (frequency). The alpha significance value was accepted as <0.05.

Results: One hundred forty seven (67.7%) of the patients were male and 70 (32.3%) were female. Ninety (41.4%) patients were operated for simple coarctation while 127 (58.6%) for coarctation and accompanying complex intra cardiac anomalies. Recoarctation was detected in 36 (16.5%) of 217 patients. Of 36 patients with recoarctation, 21 (58.3%) were treated with balloon angioplasty, 10 (27.7%) surgically, and 5 (13.8%) with stent implantation.

Conclusion: Development of recoarctation was found to be statistically significant in the patient group whose body weight was <3 kg and age was <1 year at the time of the first coarctation repair. No statistical significance was found among the surgical techniques that were used in the first coarctation repair. It is necessary to be more careful in terms of recoarctation during follow-up of the patients whose body weight was under 3 kg and whose age was under 1 year during the first coarctation repair.

Keywords: Aortic coarctation, coarctation repair, recoarctation, surgical technique

ÖZ

Amaç: Çalışmamızda, aort koarktasyonu (AK) tanısıyla opere edilmiş hastalarda rekoarktasyon gelişimi üzerine etki eden faktörler araştırılmış ve elde edilen sonuçlar ışığında, rekoarktasyon oranlarının azaltılmasına katkıda bulunulması hedeflenmiştir.

Gereç ve Yöntem: Bu retrospektif çalışmaya, Hacettepe Üniversitesi Tıp Fakültesi Kalp ve Damar Cerrahisi Kliniği'nde 1977-2010 arasında AK tanısıyla cerrahi düzeltme yapılan 358 hastadan, verilerine tam olarak ulaşılabilen ve düzenli olarak takiplerine gelmiş olan 217 hasta dahil edildi. Rekoarktasyon gelişen olgularda cerrahi düzeltme esnasındaki yaş, vücut ağırlığı ve kullanılan cerrahi tekniklerin sonuçları karşılaştırıldı. Veriler istatistiksel olarak değerlendirildi. Kategorik değişkenler için tanımlayıcı istatistikler sayı (n) ve yüzde (%) olarak belirtildi. Sonuçlar ortalama±standart sapma ve/veya yüzde (frekans) cinsinden sunuldu. Alfa anlamlılık değeri <0,05 olarak kabul edildi.

Bulgular: Hastaların 147'si (%67,7) erkek, 70'i (%32,3) kadındı. Doksan (%41,4) hasta basit koarktasyon, 127 (%58,6) hasta ise koarktasyon ve eşlik eden kompleks intrakardiyak anomaliler tanılarını ile opere edildi. Otuz altı hastada (%16,5) rekoarktasyon tespit edildi. Rekoarktasyon tespit edilen 36 hastadan 21'i (%58,3) balon anjiyoplasti, 10'u (%27,7) cerrahi, 5'i stent implantasyonu (%13,8) ile tedavi edildi.

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Sunulduğu Kongre: Çalışmamız, "Recurrence rate of surgical repair techniques for coarctation of aorta: A 33-years experience" adı altında 16. Türk Kalp ve Damar Cerrahisi Derneği E-Kongresi'nde 12.11.2020 tarihinde SS-087 kayıt numarası ile "Sözel Bildiri" olarak sunulmuştur.

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Sonuç: Çalışmamızda vücut ağırlığı <3 kg ve yaşı <1 yaş olan hasta grubunda rekoarktasyon gelişimi istatistiksel olarak anlamlı bulunmuştur. Kullanılan cerrahi teknikler arasındaysa istatistiksel bir anlam tespit edilmemiştir. AK nedeni ile opere edilecek hasta gruplarında vücut ağırlığı <3 kg ve yaşı <1 yaş olan hasta gruplarının post operatif takiplerinde rekoarktasyon gelişimi açısından daha dikkatli olunması gerekmektedir.

Anahtar Kelimeler: Aort koarktasyonu, koarktasyon tamiri, rekoarktasyon, cerrahi teknik

INTRODUCTION

Aortic coarctation (AC) is a discrete narrowing at the entry of the ductus arteriosus of the proximal thoracic aorta, that is, in the aortic isthmus region, with a frequency of 98%. AC constitutes 5-8% of all congenital heart diseases and is more common in males¹. It is the second most common cardiovascular anomaly requiring surgical intervention in the newborn period². AC was first described by Morgagni in an autopsy in 1760. The first successful AC repair was performed by Craaford and Nylin³ in 1945.

Recoarctation is defined as the presence of a resting gradient greater than 20 mmHg in the area of AC repair. Rates ranging from 4% to 20% have been reported in various series⁴. Recoarctation emerges as a complication of surgical correction and is directly related to long-term morbidity.

Age, body weight and the surgical technique used at the time of the first operation are among the main factors affecting the development of recoarctation^{5,6}. In this study, the factors affecting the development of recoarctation in patients who had been operated for the diagnosis of AC were investigated and it was aimed to contribute to the reduction of recoarctation rates in the light of the results obtained.

MATERIALS AND METHODS

Selection and Description of Cases

Of 358 patients who had undergone surgical correction with the diagnosis of AC at Hacettepe University Faculty of Medicine, Department of Cardiovascular Surgery between 1977 and 2010, 217 patients whose data could be accessed and who had regular follow-up visits were included in this retrospective study.

Patients with a peak gradient >20 mmHg in transthoracic echocardiographic (TTE) and angiographic measurements were considered as the recoarctation group. Diagnostic cardiac catheterization was performed in all patients with recoarctation as TTE in the controls. After the cases with recoarctation were identified, these cases were categorized in terms of age, body weight and surgical techniques used at the time of the first surgical correction.

The patients were divided into 3 groups considering age distribution, as 0-1 years, 1-5 years and >5 years. In terms of body weight distribution, they were divided into 3 groups, as

0-3 kilograms (kg), 3-10 kg and >10 kg. Six different surgical techniques were used in the coarctation repair surgeries of the patients. Before starting the study, permission was obtained from the Ethics Committee of Hacettepe University Faculty of Medicine (decision number: 02/10, date: 07.01.2010).

Surgical Technique

While 177 of the 217 patients included in the study were operated with left posterolateral thoracotomy, sternotomy was used in 40 patients. The patients operated with sternotomy were included in the group of patients with a hemodynamically and clinically significant and correctable intracardiac pathology accompanying coarctation, and all were operated on with the support of cardiopulmonary bypass (CPB).

Of these patients, simultaneous closure of ventricular septal defect was performed in 12 patients, intervention in congenital mitral stenosis in 9 patients, aortic arch reconstruction in 7 patients, aortic commissurotomy in 6 patients, partial pulmonary venous return anomaly correction in 3 patients, arterial switch in 2 patients and central shunt operation in 1 patient. All 7 patients who underwent aortic arch reconstruction were operated under total circulatory arrest (TSA).

Standard aortic and bicaval venous cannulation was performed in all patients operated with sternotomy. Following the transition to CPB, AC was first intervened. Following the division of the patent ductus arteriosus, all aortic tissue was released from the aortic arch to the descending thoracic aorta. Meanwhile, all intercostal arterial branches and the phrenic nerve were preserved. After the distal and proximal clamps were placed, the coarctation area and ductal tissue remnants were completely resected.

Following extensive mobilization, the distal end of the aortic arch was anastomosed to the proximal end of the descending thoracic aorta end-to-end with 7.0 polypropylene (pp) suture material. TSA was used in 7 patients with aortic arch hypoplasia. The mean TSA times were 24.8 minutes (range 18-33 minutes). In patients who underwent posterolateral thoracotomy, the thoracic cavity was entered through the left fourth intercostal space, and the mediastinal pleura was opened after retraction of the left lung upper lobe. The coarctate segment was explored, preserving all collateral lateral branches. For concomitant patent ductus arteriosus, division was used in 23 patients and double ligation-transfixion methods were used in 18 patients.

After the resection of the coarctate segment and the placement of proximal and distal vascular clamps with the end-to-end anastomosis technique, the coarctate segment was resected and end-to-end anastomosis was completed with continuous suture in the posterior aortic wall and with interrupted suture in the anterior aortic wall, using a 7.0 pp suture material.

In the extended end-to-end anastomosis technique, the aortic arch and the distal thoracic aorta were radically dissected and released. In this way, it was ensured that there was no tension in the anastomosis line. After the division of the first intercostal artery was completed, proximal and distal vascular clamps were placed. After complete resection of the coarctate segment, anastomoses were completed with 7.0 pp suture material.

In the subclavian flap aortoplasty method, the left subclavian artery was ligated proximal to its all branches in order to preserve the collateral circulation feeding the left upper extremity. A vascular clamp was placed proximally to control the transverse aortic arch, left common carotid artery and left subclavian artery. The distal vascular clamp was placed as far as possible from the coarctate segment.

The left subclavian artery was opened longitudinally along its anterior wall, and after this incision was extended to 1 cm distal to the coarctate segment, the left subclavian artery was transected. Anastomosis was completed with continuous suture technique using 7.0 pp suture material.

In the modified subclavian flap aortoplasty technique, all branches of the left subclavian artery except the internal thoracic branch were performed ligation and division. After making sure that the left subclavian artery could extended up to 2 cm distal to the coarctate segment, the transverse aortic arch, left subclavian artery and distal aorta were clamped. Beginning proximal to the left subclavian artery, an arteriotomy was performed on its anterior face, and this arteriotomy was extended up to 2 cm distal to the coarctate segment. Anastomosis was completed with continuous suture technique using 7.0 pp suture material.

In the patch aortoplasty technique, after the proximal and distal thoracic aorta was released, proximal and distal control was achieved with the help of vascular clamps. After the coarctate segment was opened longitudinally, the anastomosis was completed with a continuous suture technique, using 7.0 pp suture material and a polytetrafluoroethylene patch material of suitable geometry.

In the graft interposition technique, following the control of the proximal and distal thoracic aorta with vascular clamps, the coarctate segment was resected, and then the anastomoses were completed with the continuous suturing technique, using 7.0 pp suture material, with both proxies of the graft of

appropriate diameter end-to-end. After it was observed that there was no residual gradient between the right radial artery and the left femoral artery in all surgical techniques, bleeding controls were completed. Following the placement of the surgical drainage tubes, the layers were closed in accordance with the anatomical planning.

Statistical Analysis

The obtained data were analyzed using the Statistical Package for the Social Sciences version 17.0 (INC., Chicago, IL, USA) software. Descriptive statistics for categorical variables were expressed as numbers (n) and percentage (%). Results are presented as mean±standard deviation, median, and/or percentage (frequency). In the categorical comparisons between the groups, the significance levels were checked with the Pearson correlation test using cross-table statistics. The Mann-Whitney U test was used for pairwise group comparisons and One-Way ANOVA test was used for multi-group comparisons of data that did not have a normal distribution. The stepwise logistic regression analysis was performed to evaluate risk factors. Alpha significance value was accepted as <0.05.

RESULTS

A total of 217 patients were included in the study. Of the patients, 147 (67.7%) were male and 70 (32.3%) were female. The mean age of the patients included in the study was 5.1 ± 4.4 years (range: 2 months-16 years), and the mean body weight was 6.2 ± 3.7 kg. The patients were followed up for a median period of 78.8 months postoperatively. Gradient measurements were made after surgical correction by performing simultaneous right radial and left femoral artery catheterization in all patients.

In any of the 217 patients included in the study, no residual gradient was detected in the measurements performed on the operating table after the correction operation was completed. The mean peak systolic gradient value detected in the recoarctation region of the patients was 56 ± 17 mmHg. The time between the first coarctation correction and the diagnosis of recoarctation was determined as 5.1 ± 2.1 months. The demographic and operative characteristics of the patients included in the study are presented in Table 1. Of the patients, 90 (41.4%) were operated with the diagnosis of simple coarctation, and 127 patients with the diagnosis of coarctation and accompanying complex intracardiac anomalies. Intracardiac anomalies accompanying coarctation are presented in Table 2.

When patients who developed recoarctation were grouped according to their body weight, it was detected that 20 of 86 patients operated between 0 and 3 kg ($p=0.013$), 14 of 108

patients operated between 3 and 10 kg and 2 of 23 patients operated at >10 kg had recoarctation.

When patients who developed recoarctation were grouped according to age distribution, recoarctation was found in 24 ($p=0.016$) of 102 patients operated at the age of <1 year, in 8 of 83 patients operated between the ages of 1 and 5 years, and in 4 of 32 patients operated at the age of >5 years.

In the evaluation made according to the surgical techniques applied to the patients, the development of recoarctation was detected in 26 of 131 patients who underwent resection and end-to-end anastomosis technique, in 3 of 24 patients who underwent patch aortoplasty, in 2 of 22 patients who underwent extended end-to-end anastomosis technique, in 4

of 17 patients who underwent graft interposition technique, and in 1 of 6 patients who underwent modified subclavian flap aortoplasty technique. Recoarctation did not develop in any of 17 patients who underwent subclavian flap aortoplasty technique.

According to the logistic regression analysis, there was no statistically significant difference between surgical techniques and the development of recoarctation. Early postoperative complications included bleeding revision in 8 patients, pneumonia in 7 patients, tracheostomy due to prolonged mechanical ventilation in 2 patients, infection in the thoracotomy incision in 2 patients, chylothorax in 1 patient, hoarseness due to n. laryngeus recurrens injury in 1 patient, left diaphragmatic paralysis due to n. phrenicus damage in 1 patient.

Of 36 patients who developed recoarctation, 21 (58.3%) were treated with balloon angioplasty, 10 (27.7%) with surgery, and 5 (13.8%) with stent implantation. Of the patients who underwent surgical intervention, graft interposition was performed between the ascending aorta and the descending aorta in 4, graft interposition between the left subclavian artery and the descending aorta in 3, and patch aortoplasty in 3 patients.

Late mortality was detected in 8 (3.6%) of 217 patients in the study group. It was found that one patient died due to early postoperative heart failure after correction surgery for the diagnosis of abnormal left coronary artery originating from the pulmonary artery that had emerged five years after the coarctation repair; one patient died due to infective endocarditis of the replaced mitral valve developing 23 years after the coarctation repair; one patient died due to hypertensive intracranial bleeding; and 5 patients died due to non-cardiac causes.

DISCUSSION

If untreated, 75% of patients diagnosed with AC have an average life expectancy of 35 years⁷. In patients who are clinically stable in newborn or infancy, surgical correction is the primary treatment option as soon as the diagnosis is established⁸. Thus, life expectancy is prolonged and additional morbidities that may develop in the long term are prevented. It has been reported that recoarctation rates are low in patients diagnosed in adulthood and in those undergoing surgical correction⁹.

Since 1945, when the first coarctation correction was made, many studies have been carried out in order to prevent complications that may occur after surgical correction, especially recoarctation. Age, body weight and the techniques used in surgical correction at the time of the first operation

Table 1. Demographic and operative characteristics of the patients

Gender (male/female)	147/70 (67.7%/32.3%)
Body weight (kg)	6.2±3.7
Age (years)	5.1±4.4
Follow-up duration (months)	78.8
Peak systolic gradient in the recoarctation area (mmHg)	56±17
Duration of surgery (minutes)	68.7±10.2
Aortic clamp time (minutes)	17.5±2.1
Length of stay in intensive care (days)	4
Length of hospitalization (days)	9
Time between coarctation surgery and diagnosis of recoarctation (months)	5.1±2.1

Table 2. Concomitant cardiac anomalies (n=127)

PDA	41 (32.2%)
Bicuspid aorta	22 (17.3%)
VSD	18 (14.1%)
Aortic stenosis	12 (9.4%)
Mitral stenosis	9 (7%)
Arcus aortic hypoplasia	7 (5.5%)
ASD	6 (4.7%)
PAPVD	3 (2.3%)
AVSD	2 (1.5%)
TGA	2 (1.5%)
PS	1 (0.7%)
c-TGA	1 (0.7%)
DORV	1 (0.7%)
TA	1 (0.7%)
ALCAPA	1 (0.7%)

PDA: Patent ductus arteriosus, VSD: Ventricular septal defect, ASD: Atrial septal defect, PAPVD: Partial anomalous pulmonary venous drainage, AVSD: Atrio-ventricular septal defect, TGA: Transposition of the great arteries, c-TGA: Corrected-transposition of the great arteries, PS: Pulmonary stenosis, DORV: Doubleoutflow right ventricular TA: Tricuspid atresia, ALCAPA: Abnormal left coronary artery originating from the pulmonary artery

were evaluated as risk factors for the development of recoarctation.

Age and body weight are the most important parameters related to the somatic growth potential of the patient and therefore the native aorta. Recoarctation rates were found to be high in patients who were operated in the neonatal period^{10,11}. In our study, it was found that recoarctation developed in 24 ($p=0.016$) of 102 patients who were operated under the age of one year.

Another factor blamed for the development of recoarctation is the patient's body weight at the time of surgery. It was found that the rate of development of recoarctation was significantly higher, especially in patients who were operated on with a body weight less than 1.5 kg¹². Results of studies evaluating age and body weight simultaneously at the time of the first operation demonstrated the rates of recoarctation to be significantly higher^{13,14}. In our study, it was found that 20 ($p=0.013$) of 86 patients who were operated under 3 kg developed recoarctation.

Many surgical techniques have been developed since 1945, when AC repair was first performed. Among these techniques, resection and end-to-end anastomosis, subclavian flap aortoplasty, patch aortoplasty, extended end-to-end anastomosis, graft interposition, and modified subclavian aortoplasty are used most commonly. Regardless of the surgical technique used, complete resection of the coarctate segment is the most important factor.

As the amount of residual tissue remaining in the aortic lumen increases, the probability of developing recoarctation also increases. In the first 40 years of the history of AC surgery, resection and end-to-end anastomosis technique was seen to be the most preferred technique especially in newborn and infant period^{15,16}. With the increase in surgical experience, especially the high recoarctation rates of the resection and end-to-end anastomosis technique have led to the development of the extended end-to-end anastomosis technique and use of this technique safely in newborns, infants and childhood in the following years¹⁷.

In this technique, the most important advantage is the complete resection of both coarctate tissue and ductal tissue remnants, and the ability to perform an extended and untensioned proximal anastomosis that preserves the growth potential of the native aorta¹⁸⁻²⁰. In the subclavian flap aortoplasty technique, the use of autologous tissue with growth potential and surgical repair without creating a circular growth defect have caused this technique to be preferred more especially in infancy^{21,22}.

Due to the possibility of impaired left upper extremity circulation in the subclavian flap aortoplasty technique, the

modified subclavian flap aortoplasty technique was developed and used with low recoarctation rates, especially in the newborn and infant period²³. The patch aortoplasty technique has been used with low recoarctation rates, in which proximal and distal clamp times are much shorter, and thus post-operative mortality and morbidity are very low²⁴.

In patients with AC diagnosed in adulthood, the possibility of recoarctation with the graft interposition technique is at the same rate as other techniques²⁵. The long-term prognosis and possible morbidity of these patients following surgical repair of AC underline the need for effective long-term follow-up²⁶.

When we compared our study with similar studies in the literature, similar recoarctation rates were found among surgical techniques. In our study, it was found that none of 17 patients who underwent subclavian flap aortoplasty technique developed recoarctation. However, the highest rate of recoarctation was found in the resection and end-to-end anastomosis technique applied in 26 of 131 patients. In our study, no statistical significance was found among surgical techniques in terms of the development of recoarctation.

Study Limitations

The limitation of our study is that it was a retrospective and single-center study.

CONCLUSION

In our study, the development of recoarctation was found to be statistically significant in patients with a body weight <3 kg and the age of <1 year and in those who were operated for the diagnosis of aortic coarctation. No statistical significance was found among the surgical techniques used in the correction surgery. In the patient groups to be operated for aortic coarctation, patients with body weight of <3 kg and age of <1 year should be more carefully monitored in terms of the development of recoarctation in post-operative follow-ups.

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Ethics

Ethics Committee Approval: This retrospective study was approved by Ethics Committee of Hacettepe University Faculty of Medicine (decision number: 02/10, date: 07.01.2010).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ş., A.Ö., M.Y., R.D., M.D., Concept: B.Ş., Design: B.Ş., A.Ö., Data Collection or Processing: B.Ş., Analysis or Interpretation: B.Ş., Literature Search: B.Ş., Writing: B.Ş.

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Evaluation of Factors Affecting the Outcomes of Strabismus Surgery and Treatment of Amblyopia

Şaşılık Cerrahisi ve Ambliyopi Tedavisi Sonuçlarını Etkileyen Faktörlerin Değerlendirilmesi

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ABSTRACT

Aim: It was aimed to determine the factors affecting outcomes in concomitant esotropia and treatment of amblyopia.

Materials and Methods: The records of 159 patients in Haydarpaşa Numune Training and Research Hospital, Clinic of Ophthalmology, Strabismus Unit were retrospectively evaluated in the study. While treatment with patching was performed in 86 patients due to amblyopia, surgical intervention was performed in the other 73 patients due to concomitant esotropia.

Results: The age at onset of treatment in Strabismic Amblyopia group was 5.1 ± 1.7 years; and the final increase in visual acuity was 4.1 ± 0.4 standard lines (0.41 ± 0.04 logMAR). The age at onset of treatment in the Strabismic Anisometropic Amblyopia group was 5.3 ± 2.1 years; and the final increase in visual acuity was 4.3 ± 0.6 standard lines (0.43 ± 0.06 logMAR). In the full-time patching group, the initial visual acuity was 0.32 ± 0.17 standard lines ($=0.50 \pm 0.21$ logMAR), and the final visual acuity was 0.76 ± 0.20 standard lines (0.13 ± 0.34 logMAR). In the part-time patching group, the initial visual acuity was 0.30 ± 0.15 standard lines (0.52 ± 0.09 logMAR), and the final visual acuity was 0.63 ± 0.20 standard lines (0.20 ± 0.34 logMAR). A strong correlation was found between the initial visual acuity level and the amount of increase in visual acuity of the patients who underwent patching therapy ($p=0.00$). Surgical success in cases with binocular single vision (80.60%) was statistically significant compared to those without binocular single vision (63.60%), ($p=0.02$; chi-square test). There was no statistically significant difference in surgical success between the non-refractive and refractive concomitant esotropia ($p>0.05$; chi-square test).

Conclusion: We believe that preoperative deviation angle alone is not sufficient as a criterion for esotropia surgery planning, and considering binocular vision and stereopsis together with a successful amblyopia treatment is important for affecting the results of strabismus surgery.

Keywords: Esotropia, amblyopia, strabismus, eyeglasses

ÖZ

Amaç: Bu çalışmanın amacı konkomitan ezotropyada ve ambliyopi tedavisinde sonuçları etkileyen faktörleri belirlemektir.

Gereç ve Yöntem: Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Göz Hastalıkları Kliniği Şaşılık Bölümü'nde 159 hastanın kayıtları retrospektif olarak çalışma kapsamına alındı. Hastaların 86'sına ambliyopi nedeni ile kapama uygulanırken, diğer 73 hastaya ise konkomitan ezotropyaya nedeni ile cerrahi tedavi uygulandı.

Bulgular: Strabismik ambliyopide tedaviye başlangıç yaşı $5,1 \pm 1,7$, sonuç görme keskinliğindeki artış ise $4,1 \pm 0,4$ standart sıra ($0,41 \pm 0,04$ logMAR) idi. Strabismik Anizometropik Ambliyopi grubunda tedaviye başlangıç yaşı $5,3 \pm 2,1$ idi. Sonuç görme keskinliğindeki artış $4,3 \pm 0,6$ standart sıra ($0,43 \pm 0,06$ logMAR) idi. Tam gün kapama yapılan grupta, başlangıç görme keskinliği ortalaması $0,32 \pm 0,17$ standart sıra ($=0,50 \pm 0,21$ logMAR) idi, bu grupta sonuç görme keskinliği $0,76 \pm 0,20$ standart sıra ($=0,13 \pm 0,34$ logMAR) olarak bulundu. Kısmi kapama yapılan grupta, başlangıç görme keskinliği ortalaması $0,30 \pm 0,15$ standart sıra ($=0,52 \pm 0,09$ logMAR) olup, tedavi sonunda $0,63 \pm 0,20$ standart sıra ($=0,20 \pm 0,34$ logMAR) olarak tespit edildi. Kapama tedavisi uygulanan hastaların başlangıç görme keskinliği düzeyi ile görme keskinliğindeki artış miktarı arasında kuvvetli bir korelasyon tespit edildi ($p=0,00$). Binoküler tek görmesi olan olgularda cerrahi başarının (%80,60) binoküler tek görmesi olmayanlara (%63,60) kıyasla istatistiksel olarak anlamlı olduğu görüldü ($p=0,02$; ki-kare testi). Non-refraktif ile refraktif ezotropyaya arasında cerrahi başarı açısından istatistiksel olarak anlamlı bir fark bulunmadı ($p>0,05$; ki-kare testi).

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Sonuç: Konkomitan ezotropeya cerrahi planlamasında preoperatif kayma açısının yeterli olmadığı, başarılı bir ambliyopi tedavisi ile birlikte binoküler görme ve stereopsisin de dikkate alınmasının şaşılık cerrahisi sonuçlarını etkilemesi açısından önemli olduğu kanaatindeyiz.

Anahtar Kelimeler: Ezotropeya, ambliyop, şaşılık, gözlük

INTRODUCTION

Childhood esotropia (ET) constitutes the strabismus group that physicians will most commonly encounter due to their high prevalence. The main factors affecting the development and course of strabismus include fusion, stereopsis, the presence of refractive errors, power of accommodation, alternation, and fixation¹. The maturation period of stereopsis is considered the first decade of life, and in this critical period, the binocularity defect impairs the maturation process of stereopsis². The prevalence of amblyopia has been reported to be between 3.0% and 3.2% in the general population³.

In a study conducted in Turkey, it was reported that 1.5% of a total of screened 823 children showed strabismus and 1.8% showed signs of amblyopia on the cover test⁴. Strabismus and amblyopia are typically considered preventable vision loss if diagnosed and treated early⁵. Strabismus affects 4% of the population and causes negative effects in many areas including quality of life and psychosocial aspects in children⁶.

Amblyopia is a unilateral or bilateral reduction in visual acuity in the entire optic axis and macula without any organic cause that can decrease vision which can be detected by physical examination⁷⁻⁹. Amblyopia develops as a result of abnormal binocular interaction and vision deprivation in the first 5 years of life, which is the sensitive period and is called the critical period and physiological reflexes such as binocular single vision, accommodation, fixation and vergence are established. In strabismus amblyopia, visual stimuli from the deviating eye undergo continuous monocular suppression, resulting in reduced visual functions and amblyopia^{1,8}. The aim of the treatment of amblyopia is to provide normal and equal vision in both eyes, and to gain binocular harmony and depth perception¹⁰. In cases diagnosed with amblyopia, different treatments including correction of refractive error, patching therapy, penalisation, pleoptic therapy and treatment with CAM, neurovision and transcorneal electrical stimulation are applied. Regardless of which method is chosen, the procedure to be done in every amblyopia case is to correct the refractive error first^{1,9,11}. Patching therapy is based on the principle of forcing the amblyopic eye to see by closing the eye doing fixation in the patient^{1,8}. While correcting the refractive error in the treatment of amblyopia is very effective even on its own, short-term patching is also as effective in the treatment as intensive patching¹². With strabismus surgery, the recovery of amblyopia and binocular vision, surgical correction of non-foveal eccentric fixation, and foveal fixation are provided¹³.

Three main goals are aimed in a case to be performed strabismus surgery; binocular single vision, better aesthetic appearance, and obtaining peripheral fusion with adequate fusional vergence amplitudes to provide orthotropia¹⁴.

MATERIALS AND METHODS

A total of 159 patients who were followed up for the diagnosis of ET and amblyopia in the Haydarpaşa Numune Training and Research Hospital, 2. Ophthalmology Clinic, Strabismus Unit between January 2001 and January 2006 were included in the study. The records of 159 patients were reviewed retrospectively, and their demographic characteristics, examination findings for strabismus, strabismus type, routine eye examination findings, applied patching therapy for amblyopia, control examination findings in those who underwent patching therapy, information on the operation performed, and post-operative control examination findings were taken into account. Our studies were carried out in accordance with the Declaration of Helsinki and with the permission of the Üsküdar University Non-Invasive Ethics Committee, numbered 61351342 (date: 26.04.2022). Patching therapy was applied to 86 of the patients due to amblyopia, and surgery was performed in other 73 patients due to ET. Eighty-six patients who were applied the patching therapy due to the diagnosis of amblyopia were evaluated in two groups, as strabismic amblyopia and strabismic anisometropic amblyopia groups. All patients had unilateral amblyopia. Seventy three patients who were followed up with the diagnosis of ET and who underwent surgery were evaluated in two groups, as non-refractive accommodative ET (high AC/A ratio) and partial refractive accommodative ET groups. The AC/A ratio was measured with the heterophoria method. Cases of partially refractive accommodative ET were defined as those whose the near deviation decreased by at least 10 Δ compared to the distant deviation when the hypermetropic refractive error was fully corrected clinically, but could not be completely eliminated. Cases of fully accommodative ET, congenital ET, alphabetic-pattern ET, incomitant ET, consecutive ET, and organic amblyopia were not included in the study. In addition, patients who had a history of previous surgery or who did not continue their follow-up examinations for at least 6 months after amblyopia treatment and surgical treatment were not included in the study. The criterion for amblyopia was accepted as the presence of difference in at least two standard lines or more (≥ 0.2 logMAR) according to the Snellen chart, between the best-corrected visual acuities in the two eyes of the same

patient¹. In all cases treated for amblyopia, visual acuities at the beginning and end of treatment were converted to logMAR equivalents, and the amount of increase in visual acuity was also calculated with logMAR values. A spherical or cylindrical refractive error difference of at least 1 diopter or more was taken as the criterion for anisometropia⁶. The refractive error in both eyes and the difference in refraction between the eyes were calculated by converting them to spherical equivalent with the formula 'spherical value + cylindrical value/2'⁶. In the patching therapy performed for the treatment of amblyopia, the rule of weeks by age was followed^{4,5}. Controls of the patching treatment were carried out in the 1st, 3rd, 6th and 12th months and the patching therapy was repeated in cases deemed necessary.

In the determination of the amount of strabismus, the amount of shift determined by the prism cover test in the primary gaze position during distant fixation (after correcting the existing hypermetropic refractive error) was taken as a basis. Postoperative first day, first week, first month and sixth month controls were again performed with the prism cover test.

The presence of binocular single vision was measured by synoptophore, titmus and TNO (random dot) tests. The results were evaluated in four groups as simultaneous perception, fusion, coarse stereopsis and stereopsis. The desired outcome in patching therapy was a vision gain of at least 2 lines or more (≥ 0.2 logMAR) according to the Snellen distance reading chart. The desired postoperative outcome was determined as $\pm 10^\Delta$ shift in the primary gaze position during distant fixation.

Bilateral regression, unilateral regression and resection, bilateral regression and resection were performed in cases that underwent surgical treatment. During surgery, the muscles were sutured to the sclera with 6.0 vicryl. The conjunctivae were closed with 8.0 silk. After surgery, 0.1% dexamethasone drops 3x1 and 0.3% ofloxacin drops 5x1 were applied to the eyes for 2 weeks.

Factors, the effects of which on the outcomes of patching therapy were investigated, included the age at onset of treatment, gender, initial visual acuity, type of amblyopia, and extent of patching performed.

On the other hand, factors whose effects on surgical treatment results were investigated were age, gender, degree of

hypermetropic refractive error, age at the onset of strabismus, degree of horizontal strabismus, the presence of binocular single vision, age at surgery, and type of strabismus.

Statistical Analysis

The results of patching treatment and surgical treatment and the relationships between these factors were evaluated with the Spearman's correlation analysis, Pearson's correlation analysis, dependent t-test and chi-square tests.

RESULTS

Of the 86 patients included in the study, 34 (39.50%) were girls and 52 (60.50%) were boys. The mean age of the patients, whose age at the onset of patching therapy ranged from 3 to 10 years, was 6.1 ± 2.1 years. The mean follow-up period was 28.7 ± 14.1 months (12-60 months).

Forty patients had strabismic amblyopia (46.50%), and 46 patients had strabismic anisometropic amblyopia (53.50%).

When the effects of the age at onset of patching therapy on final visual acuity were examined, it was seen that the effect of age at onset of treatment on final visual acuity was statistically significant in both patient groups ($r = -0.240$ $p = 0.012$ in strabismic amblyopia; $r = -0.720$ $p = 0.030$ in strabismic anisometropic amblyopia); Spearman's correlation analysis) (Table 1).

Full-time patching (24 hours) was applied to 45 patients, and part-time patching (4 hours) was applied to 41 patients. The mean initial visual acuity of the patients who underwent full-time patching therapy was 0.32 ± 0.17 Snellen line ($= 0.50 \pm 0.21$ logMAR), and it was 0.76 ± 0.20 ($= 0.13 \pm 0.34$ logMAR) at the end of the treatment. In patients who underwent part-time patching therapy, the mean initial visual acuity was 0.30 ± 0.15 ($= 0.52 \pm 0.09$ logMAR), and it was 0.63 ± 0.20 ($= 0.20 \pm 0.34$ logMAR) at the end of the treatment. The levels of increase in final visual acuity of the groups were statistically significant ($p = 0.000$, $p = 0.000$, respectively; dependent t-test) (Table 2). The statistical significance shows that both patching techniques are effective methods in the treatment of amblyopia.

A strong correlation was found between the initial visual acuity level and the amount of increase in visual acuity in patients

Table 1. Effect of the age at onset of treatment on visual acuity

Patient group	Age at onset of treatment	Increase in visual acuity	p value
Strabismic amblyopia	5.1 ± 1.7	4.1 ± 0.4 standard line (0.41 ± 0.04 logMAR)	$r = -0.240$ $p = 0.012$ (significant)
Strabismic anisometropic amblyopia	5.3 ± 2.0	4.3 ± 0.6 standard line (0.43 ± 0.06 logMAR)	$r = -0.720$ $p = 0.030$ (significant)

$p =$ Spearman's correlation analysis

who underwent patching therapy ($r=0.639$, $p=0.000$; Pearson's correlation analysis).

When the success rates at the end of patching therapy were separately examined in terms of amblyopia types (cases with 2 standard lines or more) (≥ 0.2 LogMAR), the success rate was 72.50% in the strabismic amblyopia group and 76.10% in the strabismic anisometropic amblyopia group. No statistically significant difference was found ($p=0.462$; chi-square test).

In the statistical analysis comparing the age at onset of patching therapy, gender, initial visual acuity, type of amblyopia, and time of patching in a day, it was observed that gender and amblyopia type did not affect the final visual acuity ($p=0.05$).

Age at onset of patching therapy, time of patching in a day, and initial visual acuity were found to have a statistically significant effect on final visual acuity ($p=0.02$, $p=0.00$, $p=0.00$, respectively).

Of the 73 patients who were included in the surgical treatment group, 40 had non-accommodative ET and 33 had partially refractive accommodative ET.

Surgical success (81.60%) in cases with binocular single vision was statistically significant compared to cases without binocular single vision (63.60%) ($p=0.02$; chi-square test).

Surgical success rate (85.10%) in cases with a horizontal strabismus of less than 50 Δ was statistically significant compared to surgical success (61.50%) in cases with a horizontal strabismus of more than 50 Δ ($p=0.01$; chi-square test).

The age at surgery ranged from 4 to 10 years in patients. There was no statistically significant difference between the age of surgery and surgical success ($p=0.05$; chi-square test).

There was no statistically significant difference in the results of successful surgical treatment in the non-refractive accommodative ET group (77.50%) and partially refractive accommodative ET group (75.75%) ($p=0.05$; chi-square test).

In statistical analyses comparing features such as age, gender, hypermetropic refractive error, binocular vision, age at onset of strabismus, amount of horizontal strabismus, age at surgery and type of strabismus in patients with and without the desired outcomes after surgery, it was seen that age, gender, degree of hypermetropic refractive error, the age of onset of strabismus, the age at surgery and the type of strabismus did

not have a statistically significant effect on the success of surgical treatment ($p=0.05$; chi-square test).

The degrees of horizontal strabismus and binocular single vision were found to have a statistically significant effect on the success of the surgery in both patient groups ($p=0.01$, $p=0.02$; chi-square test, respectively).

Statistical significance is due to the higher surgical success in patients with binocular single vision, and the lower surgical success in patients with higher horizontal strabismus.

DISCUSSION

Childhood esodeviations (2-5%) and amblyopia (1-5%) are the most common strabismus problems¹⁵. There is no consensus on which factors affect the outcome of the surgery most, both motor and functional. Therefore, due to many factors, surgery for the treatment of strabismus and the factors affecting it affect the results of strabismus surgery¹⁶.

It has been determined that patching is more effective than glasses in children aged 3-7 years with moderate to severe amblyopia. It has been reported that additional patching will be beneficial in children with increased visual acuity using only glasses¹⁷. There is no definitively accepted formula for patching therapy in the treatment of amblyopia. Although the duration of patching therapy is usually determined in weeks according to age, the exact duration is determined by the physician according to the patient's response to the treatment. It is generally appropriate to continue the patching therapy until the vision is equal in both eyes or until it is determined that the vision does not improve in the amblyopic eye within a period of at least 3 months¹⁸. The duration of the patching therapy should be determined according to the severity of the vision loss and the age of the child¹⁹. There are no strict rules for the patching therapy to be done during the day. Full-time or part-time treatment is adjusted according to the patient's response to treatment. Depending on the response to treatment, patching can be repeated several times. When the desired level of vision is reached, patching therapy should be reduced in a controlled manner in order to maintain this situation. This therapy can be continued until the age of 10-12 years within the framework of these rules¹⁸. The patient's age plays an important role in the response to patching therapy. The first 5 years of age is the advantageous period. In patching therapies started after this age, the increase in vision becomes more and more difficult⁹. One of the biggest difficulties

Table 2. Change in visual acuity (logMAR) according to times of patching therapy

Patient group	Initial visual acuity	Final visual acuity	p value
Full-time patching (n=45)	0.50 $\pm$ 0.21	0.13 $\pm$ 0.34	$p=0.000$
Part-time patching (n=41)	0.52 $\pm$ 0.09	0.20 $\pm$ 0.34	$p=0.000$

of patching therapy is compliance with the treatment. In a study conducted by Scott et al.²⁰, patients were electronically monitored during patching therapy and it was reported that the rate of compliance with the therapy was 63%. In our study, the success rates in patching therapy for amblyopia were determined as 72.50% in strabismic amblyopia, 76.10% in strabismic anisometropic amblyopia, and 74.40% in all patients, and these values were found to be consistent with other studies. In various studies investigating the results of patching therapy in esotropia, success rates were reported as 80.30%, 85.20%, and 83%, respectively²¹⁻²³. Our study showed that the level of visual acuity improvement obtained in full-time patching was higher than in part-time patching.

In our study, it was detected that the lower the initial visual acuity, the greater the increase in visual acuity, and our results were found to be compatible with other studies²⁴⁻²⁶.

In our study, the finding of that the type of amblyopia did not make a significant difference in the increase in visual acuity after patching therapy was also found to be consistent with other studies^{20,22,26}.

The aim of strabismus surgery is primarily functional and then cosmetic correction of the deviation²⁷. The surgical success rate was 77.50% in non-refractive accommodative esotropia, 75.75% in partially refractive accommodative esotropia, and 76.60% in all patients. These results are consistent with studies in which success rates were reported as 61.90%, 63.3%, 72.90%, 76.10%, and 92.30%, respectively²⁸⁻³². It was seen that the degree of deviation angle before surgery affected the surgical results significantly in both ET groups and this result was consistent with the results of other studies. Among the factors affecting the outcome in strabismus surgery, it was reported that the most important one was the preoperative deviation angle³³. In our study, it was observed that factors such as age at surgery, gender, age at onset of strabismus, and degree of refractive error were not effective on the surgical outcome in both groups. On the contrary, it was determined that the degree of horizontal strabismus and the presence of binocular single vision in both groups affected the surgical results statistically significantly. This result was also supported by similar studies²⁸. The finding that binocular single vision is an important factor affecting the results of surgery, obtained as a result of our study, has also been shown in other studies^{34,35}.

Study Limitations

The limitations of this study include that it had a retrospective design and that it was a single-center study.

CONCLUSION

It was observed that the age range of 3-10 years was the most important period in the treatment of amblyopia, and gender

and type of amblyopia did not affect the outcome. Factors determining visual acuity as a result of patching therapy were revealed to be the age at onset of treatment, the amount of patching during the day, and initial visual acuity. In the comparison of full-time or part-time patching, there was a statistically significant difference in full-time patching, while other studies have reported that part-time patching is as effective as full-time patching. Surgical success rate was found to be 76.70% in patients who underwent surgery. It was seen that the amount of horizontal strabismus and the presence of binocular single vision affected the success of the surgeries significantly.

We suggest that preoperative deviation angle alone is not sufficient as a criterion for planning esotropia surgery, and binocular vision and stereopsis in addition to successful amblyopia treatment are important data affecting the results of strabismus surgery.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Üsküdar University Non-Invasive Ethics Committee (decision number: 61351342, date: 26.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.G., İ.Ş., Design: U.G., İ.Ş., Data Collection or Processing: U.G., İ.Ş., Analysis or Interpretation: U.G., İ.Ş., Literature Search: U.G., İ.Ş., Writing: U.G., İ.Ş.

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

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Level of Smoking Addiction and Affecting Factors in Nursing Students

Hemşirelik Öğrencilerinin Sigara Bağımlılık Düzeyi ve Etkileyen Faktörler

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ABSTRACT

Aim: This study aims to determine the smoking and nicotine addiction levels and their affecting factors among nursing students.

Materials and Methods: The study was conducted between November and December 2019, with 247 nursing students who agreed to participate in the study. The data were collected using an introductory information form and the Fagerström test for nicotine dependence. The data were evaluated using the chi-square test, one of the descriptive and univariate analyses, and analyzed using the Statistical Package for the Social Sciences 20.0 software.

Results: Of the nursing students, 61.9% were female. The males (38.3%) had higher levels of smoking than the females. Those aged 21 years and above (12.1%) had higher levels of smoking than those between 17-20 years of age ($p<0.05$). In addition, the first-year students (8.0%) had lower levels of smoking than other students. Cigarette use was lower in nursing students who knew the harms of smoking (18.6%) compared to those who did not know ($p<0.05$). It was higher in those who had retaken a failed course and in those who had a smoker in their family (25.3%) or friend circle (24.9%) ($p<0.05$). Education and other smoking characteristics had no effect on smoking status ($p>0.05$). Of the nursing students who smoked, 92.9% had a very advanced level of nicotine addiction.

Conclusion: Smoking status is negatively affected by being male, age, retaking a failed course, having a friend who is a smoker, having a smoker in the family, and considering smoking as harmless to health.

Keywords: Nursing students, smoking, nicotine, tobacco

ÖZ

Amaç: Çalışmanın amacı üniversite öğrencilerinin sigara kullanımı ve nikotin bağımlılık düzeylerini belirlemek, sigara kullanımında ve nikotin bağımlılığında etkili olan faktörleri ortaya koymaktır.

Gereç ve Yöntem: Araştırma Kasım-Aralık 2019 tarihleri arasında bir üniversitenin hemşirelik bölümünde öğrenim gören ve çalışmaya katılmayı kabul eden 247 hemşirelik öğrencisi ile yürütülmüştür. Verilerin toplanmasında tanıtıcı bilgi formu, Fagerström nikotin bağımlılık testi kullanılmıştır. Araştırmada tanımlayıcı analizler ve tek değişkenli analizlerden ki-kare testi uygulanmıştır. Veri analizinde Statistical Package for the Social Sciences 20.0 istatistik paket programı kullanılmıştır.

Bulgular: Araştırmaya katılanların %61,9'u kadındı. Erkek cinsiyette sigara kullanım düzeyi %38,3 ile kadın cinsiyetten; 21 yaş ve üzeri grupta ise %12,1 ile 17-20 yaş aralığındaki öğrencilerden daha yüksekti ($p<0,05$). Sigara kullanımı oranı birinci sınıf öğrencilerinde %8,0 ile diğer sınıflardaki öğrencilerden, sigaranın zararlarını bilenlerde %18,6 ile bilmeyenlerden daha düşüktü ($p<0,05$). Altan dersi olanlarda, ailesinde (%25,3) ve arkadaş çevresinde (%24,9) sigara kullanımının mevcut bulunduğu kişilerde sigara kullanımı daha yüksek bulundu ($p<0,05$). Eğitim ve sigara içmeye ait diğer özelliklerin sigara kullanım durumu üzerinde etkisi bulunmamaktadır ($p>0,05$). Sigara kullanan öğrencilerin %92,9'unda çok ileri düzeyde nikotin bağımlılığı bulunmaktadır.

Sonuç: Sigara kullanım durumunu erkek olma, yaş, başarısızlığa bağlı ders tekrar etme, arkadaş çevresinde sigara kullanımı, ailede sigara kullanan bireylerin varlığı, sigaranın sağlığa zarar vermeyeceğini düşünme gibi faktörler olumsuz yönde etkilemektedir.

Anahtar Kelimeler: Hemşirelik öğrencileri, sigara, nikotin, tütün

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INTRODUCTION

The behavior of smoking is affected by genetic, neurobiological, demographic, and psychological factors. Childhood experiences can cause this behavior^{1,2}. Addiction refers to physiological, cognitive, and behavioral changes that occur after repeated substance use³. Nicotine relieves stress and causes a feeling of pleasure. By quitting smoking, dopamine levels decrease, and the desire to smoke appears^{4,5}. Most smokers are trying to cope with stress. As stress causes acid production, nicotine withdrawal symptoms occur in the body².

Tobacco addiction, which is a social problem, causes the death of one person every six seconds worldwide. In addition, more than 600,000 non-smokers die every year due to passive smoking. There are 1.1 billion tobacco users in the world, and this number is expected to reach 1.6 billion in the next 20 years. Smoking causes lung and heart diseases, sudden death syndrome in infancy, and miscarriage in pregnant women^{4,6,7}. However, the prevalence of smoking still increases even though people know its harmful effects. If relevant measures are not taken, the number of smoking-induced deaths is estimated to exceed 10 million by 2030^{8,9}.

Tobacco use in individuals aged 15 years and over was 26.5% in 2016 and 28% in 2019 in Turkey. The rate of tobacco use by women was 13.3% in 2016 and 14.9% in 2019; 14.9% of women use tobacco every day^{10,11}. According to TURKSTAT (2019) data, daily cigarette use by individuals aged 15–24 years has increased to 18.1%¹¹. World Health Organization (2018) reported the rate of smoking in males over 15 years of age as 35.6% in France, 33.7% in Japan, 33.1% in Germany, and 41.1% in Turkey¹². TURKSTAT (2019) reported “peer influence” as the most common cause of starting to smoke in those over the age of 15 years¹¹.

Smoking in young people is facilitated and reinforced by certain factors such as individual's age, income, acculturation, stress, and environmental factors including tobacco advertising and ease of purchase of tobacco products^{13–15}. Starting and continuing to smoke cigarettes in adolescence arises from wanting to feel appreciated, fitting in socially, and through the influence of friends¹⁶.

A person's university years are a period of rapid life changes, new friendships, and social sharing. University students may struggle with several problems accompanying these new life changes and being away from family and relatives¹⁶. There are several studies on the smoking addiction of university students^{17,18}. However, this study is on those students who have a low level of income and need qualified health practices the most¹⁹. This study aimed to determine the smoking and nicotine addiction levels and affecting factors in nursing students.

MATERIALS AND METHODS

Type of Study

This is a descriptive study.

Place and Time of Study

The study was conducted with nursing students at a university in Turkey between November and December 2019. The sample size was aimed to include 260 nursing students. However, 247 nursing students who were in the nursing faculty during the course of the study and who agreed to participate were included in the study.

Study Inclusion Criteria

Nursing students who did not have any sensory, mental, or physical disabilities or communication problems and signed the informed consent form were included in the study.

Data Collection Tools

The data were collected using a structured questionnaire form prepared by the researcher in line with the literature and the Fagerström test for nicotine dependence (FTND)²⁰.

Structured Questionnaire Form

The form included questions about nursing students' socio-demographic and family characteristics, university education, and smoking status.

Fagerström Test for Nicotine Dependence

The FTND is used in smoking cessation clinics^{21,22}. It was developed by Fagerstrom et al.²³ (1992) and it consists of six questions. There are 2 or 4 answer options for the questions. Three of the questions are in the form of yes-no, and they have two answer options. Point value is zero or one. Three of them are in the form of multiple choice answers, they have four answer options and the point value is between zero and three. As the level of addiction to cigarette increases, the score obtained from the test also increases. The highest score that can be obtained from the test is 10, and the lowest score is 0.24. The FTND scoring is evaluated as low (0–4 points), medium (5–6 points), high (7–8 points) and very high (9–10 points)²⁴. The Turkish validity and reliability study of the FTND was performed by Uysal et al.²⁰ (2004), who found it moderately reliable. The Cronbach's alpha coefficient of the scale was determined as 0.56²⁰.

Research Variables

The dependent variable was the level of smoking. The independent variables were gender, age, family type, education and employment status of parents, place of residence during university education, grade, status of retaking a failed course,

smoking of family and friends, and the status of knowing the harmful effects of smoking.

Statistical Analysis

The data were evaluated using s descriptive analysis (number, percentage, mean, standard deviation) and chi-square test and then analyzed using the Statistical Package for the Social Sciences 20.0 statistical program. The researchers covered all research expenses. A p value less than 0.05 was considered statistically significant.

Data Collection

The data were collected in the classroom environment by face-to-face interview technique. It was collected within 15-20 minutes. Before starting to collect data, students were informed about the research.

Ethical Considerations

For conducting the study, ethical approval (decision no: E.17798, date: 25.12.2019) was obtained from the Non-Interventional Ethics Committee of the Muş Alparslan University and written permission from the institution where the study was conducted. In addition, an Informed Consent Form was received from nursing students who agreed to participate in the study. Confidentiality of the data was ensured.

RESULTS

Of the nursing students, 61.9% were female, 50.2% were between 17 and 20 years old, 23.1% had extended family, and 31.6% had an income less than their expenses. 49.0% of their fathers and 2.0% of their mothers were employed, and 73.3% of their mothers, and 31.6% of their fathers were illiterate or did not go to school. The males (38.3%) had higher levels of smoking than the females. The students aged 21 years and above (12.1%) had higher levels of smoking than those aged 17-20 years ($p<0.05$). Other socio-demographic variables had no effect on the level of smoking ($p>0.05$) (Table 1).

62.8% of the nursing students lived in dormitories during their university education, 35.2% were first year students, 33.6% retook a failed course, 83.0% had smokers in their circle of friends, 67.2% had smokers in their families, and 95.5% knew the harmful effects of smoking (Table 2).

The first year students (8.0%) had lower levels of smoking than those who returned back to school. Cigarette use was lower in nursing students who knew the harms of smoking (18.6%) compared to those who did not know ($p<0.05$). It was higher in those who retook a failed course and in those who had a smoker in their families (25.3%) or friend circle (24.9%) ($p<0.05$) (Table 2).

The rate of smoking in nursing students was 20.6%. Of the smokers, 54.9% started smoking in high school and 23.5% in

university; 43.1% started smoking to prove themselves adults, 56.9% smoked in stressful situations, and 44.2% did not want to quit smoking (Table 3).

The average FTND score of the nursing students was 12.7 ± 2.6 . Of the smokers, 92.9% had a very advanced level of nicotine addiction.

DISCUSSION

University years are one of the most critical periods when individuals start to smoke. This study was conducted in a region where students live mostly in dormitories and have insufficient income. Smoking nursing students reported to have started smoking most frequently during high school years, followed by university years. The age of smoking is gradually decreasing throughout Turkey²⁵.

Most of the cigarette addicted-adults started smoking before the age of 18 years^{6,15,26}. Studies have determined that the age of starting to smoke decreases as low as 13 years^{1,27}. This shows that smoking can begin in childhood and that although the sale of tobacco is prohibited, it is easily accessible for children. People who start smoking in childhood become addicted during their university years. Our study found the level of smoking in nursing students as 20.6%. Several studies found the smoking rate ranging from 12.3% to 30.0% in Turkey^{1,25,28,29}. Comparable results have been observed in other countries; smoking levels of nursing students in countries such as France, the USA, Spain, and Australia vary between 22.9% and 30.4%^{30,31}.

In the present study, smoking nursing students started smoking most frequently to prove themselves adults. Studies report that individuals start smoking due to several reasons such as lack of family support, school problems, loneliness, influence from a friend, and curiosity^{10,27,30}. In the present study, other reasons for starting smoking in nursing students were academic stress, wanting to be like friends, curiosity, and the presence of smokers in the family. Showing themselves as grown-ups, adapting to their social-school environment, and attracting attention were some of the reasons why these nurses started smoking, many of whom were young when they began³²⁻³⁵.

In many societies, smoking is a socially accepted behavior in men. The tobacco industry aims to increase men's cigarette consumption by turning this social acceptance into an opportunity. Several studies found higher levels of smoking in males than in females³⁶⁻³⁸. Our study also found higher levels of smoking in male nursing students than in female ones. In recent years, the smoking habit among women has increased rapidly. This is associated with women's more active participation in social life due to their university education. The new target audience of the tobacco industry, which considers that men's cigarette consumption has reached the desired level, has become women. Therefore, tobacco companies have increased their marketing activities encouraging women to start smoking³⁸.

Table 1. Distribution of sociodemographic variables by smoking status

	Status of smoking						
	Yes		No				
Characteristics	N	%**	N	%**	%*	χ ²	P
Sex							
Female	15	9.8	138	90.2	61.9		
Male	36	38.3	58	61.7	38.1	27.14	<0.01
Age							
17-20 years	15	12.1	109	87.9	50.2		
21 years and above	36	29.3	87	70.7	49.8	10.08	<0.01
Type of family							
Extended	14	24.6	43	75.4	23.1		
Nuclear	37	19.5	153	80.5	76.9	0.417	0.52
Income level							
Low	11	14.1	67	85.9	31.6		
Balanced	34	22.5	117	77.5	61.1		
High	6	33.3	12	66.7	7.3	4.129 ^a	0.13
Father's employment status							
Employed	25	20.7	96	79.3	49.0		
Unemployed	26	20.6	100	79.4	51.0	0.00	1.00
Mother's employment status							
Employed	0	0.0	5	100.0	2.0		
Unemployed	51	21.1	191	78.9	98.0	***	0.59
Mother's education level							
Does not know Turkish	6	24.0	19	76.0	10.1		
Illiterate	17	17.0	83	83.0	40.5		
Literate	13	23.2	43	76.8	22.7		
Primary school	6	17.1	29	82.9	14.2		
Secondary school	8	30.8	18	69.2	10.5		
High school	1	20.0	4	80.0	2.0	3.098 ^a	0.69
Father's education level							
Literate	18	23.1	60	76.9	31.6		
Primary school	9	18.0	41	82.0	20.2		
Secondary school	10	16.9	49	83.1	23.9		
High school	10	23.3	33	76.7	17.4		
University and above	4	23.5	13	76.5	6.9	1.252 ^a	0.87
*Column percentage, **Row percentage, ***Fisher's chi-square test, ****The group causing the difference, ^a Chi-square test value							

*Column percentage, **Row percentage, ***Fisher's chi-square test, ****The group causing the difference, ^aChi-square test value

Age also affects smoking. In this study, the level of tobacco use increased as the age of nursing students increased. Changes in the social environment and increased stress due to age increase smoking rates³⁹. Moreover, after reaching a certain age, it becomes difficult for individuals to quit this habit²⁶. As the nursing students progress in their studies, differences in smoking behaviors for the different years of study occur. Studies have shown that senior nursing students are more likely to be smokers^{24,40-42}. The present study found the smoking level lower in first-year nursing students than in other classes. This result suggests that health education does not change

nursing students' unhealthy habits; as their grade progressed, their tendency to smoke increased. An increased number of people with bad habits like smoking and alcohol use due to extended social circles of higher-year students is effective in smoking behaviors³⁹. In particular, the stress of graduation and finding a job increases smoking, especially in senior nursing students.

Having a failed course and low academic success has a significant effect on the stress of nursing students, increasing their tendency to smoke. Our study found higher smoking habits in nursing students who retaken a failed course than

Table 2. Distribution of education and smoking variables by smoking status

	Status of smoking						
	Yes		No				
Characteristics	N	%**	N	%**	%*	χ^2	p
Place of residence							
House	9	33.3	18	66.7	10.9		
Dorm	26	16.8	129	83.2	62.8		
Family home	16	24.6	49	75.4	26.3	4.669 ^a	0.09
Year							
1. year****	7	8.0	80	92.0	35.2		
2. year	10	20.0	40	80.0	20.2		
3. year	11	20.8	42	79.2	21.5		
4. year	23	40.4	34	59.6	23.1	21.95 ^a	<0.01
Status of retaking a failed course							
No	15	9.1	149	90.9	66.4		
Yes	36	43.4	47	56.6	33.6	37.34	<0.01
Status of having a smoker in the circle of friends							
Yes	51	24.9	154	75.1	83.0		
No	0	0.0	42	100.0	17.0	11.69	<0.01
Status of having a smoker in the family							
Yes	42	25.3	124	74.7	67.2		
No	9	11.1	72	88.9	32.8	5.85	0.02
Status of knowing the harmful effects of smoking							
Yes	44	18.6	192	81.4	95.5		
No	7	63.6	4	36.4	4.5	***	<0.01
*Column percentage, **Row percentage, ***Fisher's chi-square test, ****The group causing the difference, ^a Chi-square test value							

*Column percentage, **Row percentage, ***Fisher's chi-square test, ****The group causing the difference, ^aChi-square test value

other students. Karabiber et al.³⁵ (2018) found a similar result, reporting an increase in tobacco use by those who repeated their courses due to failure.

Having a smoker in the family, friends, or peers is a disadvantage in terms of starting smoking⁴³⁻⁴⁷. In this situation, it causes them to perceive cigarette as a harmless substance. In this study, nursing students who had a smoker in their family or close friend circle smoked more than other students. Several studies have found comparable results, reporting a high level of cigarette addiction in nursing students whose family members or classmates smoked⁴⁸⁻⁵⁰. Kutlu et al.³⁸ (2005) found a significant relationship between one's smoking status and the smoking status of close friends, fathers, and siblings. This may be because they see smoking family members as role models, emulate their circle of smoking friends and do so since childhood.

Knowing the harmful effects of smoking is a key factor that protects people from this habit. This study determined that nursing students who did not know the harmful effects of smoking smoked more than other students. Although the majority of the students know about the harmful effects of smoking, 44.2% of them did not want to quit smoking. This shows that despite their education, they did not have a sufficient level of consciousness about the subject⁵¹. An early start to smoking and resistance to quitting increases cigarette addiction⁵².

One of the principal factors affecting the success of quitting smoking is the severity of nicotine addiction⁵³. In the present study, the average FTND score of the nursing students was 12.7 ± 2.6 . Of the smokers, 92.9% had a very advanced level of nicotine addiction. These results are well above those in the literature. Battaloğlu İnanç²⁸ (2015) found that the mean FTND score was 3.08 ± 2.07 , and 20.0% of the participants had advanced and 5% had very advanced levels of nicotine addiction. The mean FTND score of the nursing students was found as 3.88 ± 2.34 by Moreno-Coutiñove and Villalobos-Gallegos⁵⁴ (2017) and 3.52 ± 2.47 by Evli et al.¹⁶ (2021). The reasons why addiction scores are higher than in the literature can be shown as smokers around, encouragement of friends and feeling of curiosity, staying away from family, seeing family as authority, and the sense of autonomy that comes with university life⁵⁵.

Study Limitations

This study has some limitations. Its results are limited to nursing students in the place and time of the study. The data were collected using self-reports of the students. The majority of the nursing students who agreed to participate in the study were women.

CONCLUSION

Smoking status is negatively affected by male gender, age, retaking a failed course, having a smoker in the circle of friends,

Table 3. Descriptive characteristics of smokers (n=51)

Characteristics	N	%
Time when they started smoking		
Primary school or before	1	2.0
Secondary school	10	19.6
High school	28	54.9
University	12	23.5
Reason for starting to smoke		
Wanted to be like a family member	3	5.9
Wanted to be like a friend	10	19.6
Academic stress	10	19.6
Curiosity	6	11.8
An effort to prove something to oneself	22	43.1
Time when they smoke mostly		
Leisurely	16	31.4
While studying	6	11.8
Under stressful situations	29	56.9
Considering quitting smoking		
Yes	29	55.8
No	23	44.2

having a smoker in the family, and considering smoking as harmless to health.

The results suggest revising education on smoking addiction. A fight against tobacco addiction should be highlighted in the curriculum of nursing faculties and continuing education centers. Club activities, certificate programs, and relevant courses are necessary for education on smoking addiction to be effective; alternative techniques, hobbies, or sport activities should be planned. Education and awareness levels of parents should be increased. Strategies to combat smoking should target both individuals and their immediate circles.

Ethics

Ethics Committee Approval: The study were approved by the Muş Alparslan University of Non-Interventional Ethics Committee (decision no: E.17798, date: 25.12.2019).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: E.B., S.G.

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Propriospinal Myoclonus in a Patient with Thoracic Disc Protrusion While Awakening from General Anesthesia: A Case Report

Torasik Disk Protrüzyonu Olan Bir Hastada Genel Anesteziden Uyanırken Görülen Propriospinal Miyoklonus: Olgu Sunumu

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ABSTRACT

Propriospinal myoclonus (PSM) is a rare clinical phenomenon that is mostly idiopathic but may be secondary to a spinal lesion. A patient who experienced PSM while awaking from general anesthesia, and who had thoracic disc protrusion, was presented. A 32-year-old male patient was taken to the dental procedure under general anesthesia. Arrhythmic flexion of the axial muscles was observed one to two times per second during and after the awaking phase. And neck flexion accompanied these movements about every ten seconds. The abnormal movements were decreased in amplitude and frequency and resolved spontaneously in about an hour. His examination and blood tests were normal, including infections. Thoracic magnetic resonance imaging with contrast agent showed left paramedian disc protrusion at the T7-T8 level. It should be kept in mind that these types of abnormal movements can be seen after anesthesia. When this is the case, structural lesions such as thoracic disc herniation should be eliminated.

Keywords: Propriospinal myoclonus, thoracic disc protrusion, general anesthesia, case report

ÖZ

Propriospinal miyoklonus (PSM), çoğunlukla idiyopatik olan ancak spinal bir lezyona sekonder de görülebilen nadir bir klinik fenomendir. Bu çalışmada genel anesteziden uyanırken PSM gözlenen ve nörogörüntüleme torakal disk protrüzyonu saptanan bir olgu sunuldu. Otuz iki yaşında erkek hasta genel anestezi altında diş tedavisine alınmıştı. Uyanma fazı sırasında ve sonrasında aksiyal kasların saniyede bir ila iki kez aritmik fleksiyonu gözlemlendi. Yaklaşık her on saniyede bir bu hareketlere boyun fleksiyonu eşlik etti. Anormal hareketler yaklaşık bir saat içinde amplitüd ve frekans olarak azalarak kendiliğinden düzeldi. Muayenesi ve enfeksiyon tetkikleri dahil kan testleri normaldi. Kontrast madde kullanılarak yapılan torakal manyetik rezonans görüntüleme T7-T8 seviyesinde sol paramedian disk protrüzyonu izlendi. Anestezi sonrası bu tür anormal hareketlerin görülebileceği akılda tutulmalıdır. Bu tür durumlarda torasik disk hernisi gibi yapısal lezyonlar ekarte edilmelidir.

Anahtar Kelimeler: Propriospinal miyoklonus, torakal disk protrüzyonu, genel anestezi, olgu sunumu

INTRODUCTION

Propriospinal myoclonus (PSM) is a rare clinical phenomenon that was first described by Brown et al.¹ in 1991. It is a type of spinal myoclonus with brief, repetitive, and mainly arrhythmic flexor axial jerks that usually spread to knees, hips, and neck as a result of slow propagation up and down the spinal cord.

Cranial muscles are usually not involved. PSM is idiopathic in almost 80% of patients but it may be functional or secondary to a spinal lesion²⁻⁴. The myoclonic generator is most commonly at the thoracic level. The jerks in symptomatic PSM usually last between 100 and 300 ms. The jerks are seen in the supine position and wake-sleep transition, which is thought to reduce

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sleep-related spinal inhibition and resulted from the activation of generators⁴.

Although acute onset PSM may be associated with a spinal lesion, there is a wide spectrum of secondary causes including ischemic myelopathy, cervical tumors, dural arteriovenous fistula, neuromyelitis optica, syringomyelia, cervical/lumbar disc pathologies with or without myelopathy, infections such as herpes zoster, neuroborreliosis, inflammation, drugs such as interferon, ciprofloxacin, intrathecal bupivacaine, and multiple drugs for cesarean section^{2,4}.

In the present study, a case who experienced PSM while awakening from general anesthesia and had thoracic disc protrusion was presented.

CASE REPORT

A 32-year-old male patient was taken to the dental procedure under general anesthesia. Midazolam 2 mg was administered as premedication. Remifentanyl 50 mcg, diprivan 200 mg, and rocuronium bromide 40 mg were administered for induction in the supine position. Remifentanyl 0.1-0.2 mcg/kg/h and sevoflurane 1% mL/min were administered during the procedure. The procedure lasted about two hours. His vital parameters were stable during the anesthesia and the awaking phase. Arrhythmic flexion of the axial muscles was observed one to two times per second during and after the awaking phase. And neck flexion accompanied these movements about every ten seconds. The abnormal movements were decreased in amplitude and frequency and resolved spontaneously in about an hour. Other drugs administered to the patient were dextetopfen, cefamezine 1 g, ranitidine, atropine 0.5 mg, and neostigmine 1.5 mg. His vital parameters were as follows;

blood pressure: 146/87 mmHg, pulse: 90/min, SpO₂: 99%, temperature: 36.3 °C while the abnormal movements were observed. There was no history of any disease or drug abuse. There was no history of autoimmune diseases in his family. The blood tests were normal, including infections. Thoracal magnetic resonance imaging (MRI) with contrast agent showed left paramedian disc protrusion at the T7-T8 level and diffuse bulging at the T11-T12 level (Figure 1). There was a wide-based disc protrusion at the L5-S1 level. No space-occupying, demyelinating lesion, or fistula was seen.

DISCUSSION

Although it is predominantly seen in middle-aged males, symptomatic PSM is seen mostly in females²⁻⁴. PSM is frequently stimulus sensitive and may originate from the propriospinal pathways, while the role of this pathway has not yet been confirmed in humans^{2,3}. Electrophysiological studies have shown that bursts start at the midthoracic segments and simultaneously propagate to the other segments of the spinal cord and jerks are variable from one to the other. Brown et al.¹ suggested a polysynaptic transmission in the ventrolateral funiculus related to slowly conducting pathways.

No lesion is detected in most of the MRIs but Roze et al.⁵ found microstructural defects in some patients using diffusion tensor imaging in the spinal cord, which was proposed as the cause of local hyperexcitability and generator of the myoclonus. Ayache et al.⁶ results pointed to the possible reticular formation involvement, which is known to produce excitation of propriospinal neurons that activate the thoracic spinal generator. It is still not clear whether the abnormalities seen on MRI are associated directly with the symptoms or reflect a process related to the primary dysfunction^{5,6}.

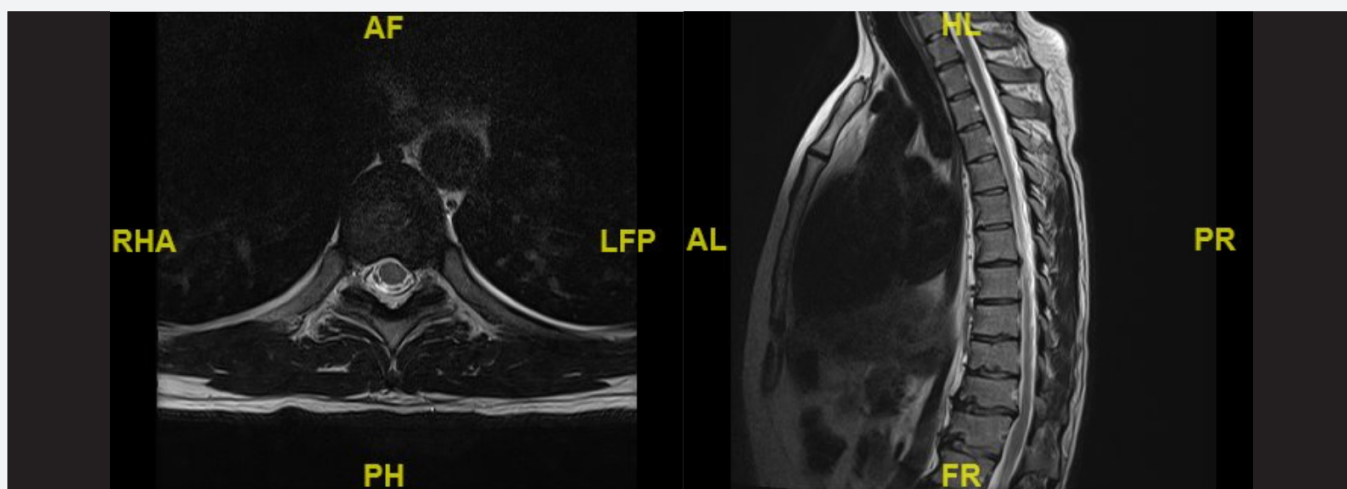


Figure 1. Left paramedian disc protrusion at the T7-T8 level on T2 axial image, disc protrusion at the T7-T8 level, and diffuse bulging at the T11-T12 level on T2 sagittal image

Spontaneous remission is a clue for the functional PSM. In this case, jerks occurred when the patient was awakening from the general anesthesia and gradually decreased and solved spontaneously without medication in half an hour. So, we could not have a chance to perform an electrophysiological study. We saw paramedian disc protrusion which caused mild compression on medulla spinalis at T7-T8 level on MRI as a cause of the PSM. Although we did not detect a structural medulla spinalis lesion on standard MRI, probably there was a functional impairment that was provoked by the anesthetic agents, as Roze et al.⁵ proposed.

CONCLUSION

In conclusion, it should be kept in mind that these kinds of abnormal movements can be seen after anesthesia. When this is the case, structural lesions such as thoracic disc herniation should be eliminated.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Informed Consent: Informed consent was taken from patient.

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