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Research Article

The Relationship of Hematologic Parameters and Lipid Profile with Acute Ischemic Stroke

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Objective: This study aims to investigate the effect of routine laboratory parameters on clinical outcomes in patients with acute ischemic stroke (AIS).

Materials and Methods: Our study was designed as retrospective and cross-sectional. 94 patients with AIS who received inpatient treatment in our clinic with a diagnosis of acute ischemic stroke were included in the study. Laboratory data, demographic, and clinical characteristics were recorded at the time of admission. Neurological disabilities of the patients 3 months after treatment were evaluated with the modified Rankin Scale (mRS). mRS 0-2 was considered a good prognosis and mRS 3-6 was considered a poor prognosis.

Results: Of the 94 patients included in the study, 47 were men and 47 were women. The mean age was 71.18±11.92 years. Laboratory parameters hemoglobin, eosinophil, total-cholesterol, ldl-cholesterol, and triglyceride values were significantly lower in the group with mRS≥3. As a result of ROC analysis, the area under the curve of hemoglobin, eosinophil, total-cholesterol, ldl-cholesterol, and triglyceride was significantly higher[(AUC: 0.710 95%CI: 0.60-0.81); Sensitivity=67.6%, Specificity=67.9%, p=0.001]. In the multivariable logistic regression model, only the NIHSS score (National Institutes Of Health Stroke Scale Scores) was independently associated with the degree of disability (p=0.001). NIHSS is an independent factor in predicting stroke outcomes.

Conclusion: It was determined that there was a significant inverse relationship between the routine laboratory parameters hemoglobin level, eosinophil level, LDL and total cholesterol levels, and infarct volume with the NIHSS scores of hemoglobin and LDL-cholesterol.

Keywords: Acute ischemic stroke, Laboratory, Infarct volume, Clinical outcome

1. INTRODUCTION

Stroke is known as an important cause of mortality and morbidity worldwide.[1,2] Patients and their relatives always worry about the negative situations that may occur after a stroke. Clinicians' prediction of post-stroke prognosis will help determine stroke management. In this respect, it is important to predict the prognosis of stroke and take the necessary precautions.[3] In previous studies, complete blood count and biochemical tests were routinely used to indicate the prognosis of stroke. Studies have reported that routine laboratory tests may be useful in taking necessary steps to prevent the negative consequences of stroke.[3,4] In general, an increase in neutrophils, total white blood cells, and a decrease in lymphocytes are common laboratory findings during inflammation.[5] There are numerous studies to evaluate the relationship between hematological parameters and cardiovascular diseases. RDW (Red Blood Cell Distribution Width) and Mean platelet volume (MPV) are reliable prognostic parameters in cardiovascular diseases. Evaluation of white blood cells, NLR (neutrophil/lymphocyte ratio), monocyte/HDL-cholesterol, and PLR (platelet/lymphocyte ratio) can predict the

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prognosis of cardiovascular diseases.[6] Complete blood count and some biochemical parameters are routinely checked in stroke patients. These tests are easily accessible and cost-effective. In this respect, predicting prognosis after stroke will be easy and low-cost. In our study, we aimed to investigate the effect of routine laboratory parameters at admission on functional outcomes after stroke.

2. METHODS

2.1.Study population

This study was designed as a retrospective and cross-sectional study. 94 patients who were admitted to our clinic from the emergency department in the first 24 hours with the diagnosis of acute ischemic stroke and then came for outpatient clinic controls for at least 3 months were included. The patients' data were retrospectively examined from the hospital database following the ethics committee and institutional permissions. Strokes other than acute ischemic stroke, patients with missing brain CT, hemogram, and biochemical examinations during hospitalization, patients without outpatient clinic follow-up after discharge, patients with systemic diseases that would affect complete blood count parameters on admission, and patients with severe sequelae motor deficits upon admission were not included in the study. In this study; A total of 94 patients, who were 18 years of age and above, came for regular check-ups at the stroke outpatient clinic during the 3-month follow-up period after discharge, and had complete clinical data, were included in the study. Neurological disabilities of the patients 3 months after treatment were evaluated with Modified Rankin Scale (mRS) scores. Patients were divided into two groups according to Modified Rankin Scale (mRS) scores. mRS 0-2 was considered a good prognosis and mRS 3-6 was considered a poor prognosis. Ethics committee approval was received for the study and the study was conducted by the Ethical Standards of the Declaration of Helsinki. Since it was a retrospective file scan, patient consent could not be obtained.

2.2. Demographic, radiological examinations and laboratory

Anamnesis information, demographic characteristics, vascular risk factors [arterial hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), Atrial Fibrillation (AF), hyperlipidemia (HL)], antiplatelet, statin, included in the prepared case report form. The presence of smoking was obtained from file data. Patients whose fasting blood sugar was 120 mg/dL and above in at least three measurements or who were previously diagnosed and received anti-diabetic treatment were diagnosed with DM. Patients who smoked at least half a pack/day and smoked for more than 1 year before the stroke were considered to be smokers. For the diagnosis of arterial hypertension, conditions were required: having been previously diagnosed and still using anti-hypertensive medication, or having an average blood pressure above 140/90 mmHg during hospitalization. HL was diagnosed in patients whose fasting blood total cholesterol and/or triglyceride levels were above 200 mg/dl or who were previously diagnosed with HL and were currently receiving anti-hyperlipidemia treatment.

Diffusion-weighted MRI (Magnetic Resonance Imaging) examinations of the patients taken at the time of initial admission were reviewed. In diffusion MRI (1.5 tesla, geo signa explorer, 2019), images were obtained using a section thickness of 4 mm. The volume of the ischemic area was calculated with the 'Region of Interest (ROI)' method in the diffusion-weighted imaging seen at the time of admission 7 and the infarct volume (cm3) was recorded.

After an overnight fast of at least 12 hours, complete blood count, total cholesterol (TC), high-density lipoprotein cholesterol (Hdl-cholesterol), low-density lipoprotein cholesterol (Ldl-cholesterol) and triglyceride (TG) concentrations, and liver and kidney function tests were measured by routine laboratory methods.

2.3. Statistical analysis

The suitability of continuous variables to normal distribution was examined with the Kolmogorov-Smirnov test. According to the results of the normality test, variables that comply with normal distribution are given with their mean and standard deviation, and variables that do not comply with normal distribution are given with their median, minimum, and maximum values. According to the normality test results, Mann Whitney U test and Independent paired sample t-test were used for intergroup comparisons of continuous variables. Categorical variables were compared between groups using the chi-square test and Fisher's exact chi-square test. The relationships between continuous variables were examined by correlation analysis and the Spearman correlation coefficient was calculated. ROC analysis was performed to determine the cut-off point for hemoglobin, eosinophil, LDL-cholesterol, and triglyceride levels to predict mRS ≥3. Factors that are effective in observing poor prognosis were examined by logistic regression analysis. SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) program was used for statistical analysis, and $p<0.05$ was considered statistically significant.

3. RESULTS

Of the 94 patients included in the study, 47 were male (50%) and 47 were female (50%). The mean age was 71.18± 11.92 years. It was determined that the incidence of hypertension, heart failure, and AF was higher in the poor prognosis group (84.2% & 46.4%; $p<0.001$, 21.1% & 5.4%; $p=0.04$, 50% & 26%, respectively). 8; $p=0.03$). Median infarct volume was also higher in the group with mRS ≥3 (11.22 & 1.37; $p<0.001$). NIHSS score was also determined to be higher in the group with mRS ≥3 ($p<0.001$). The mean age was also higher in the group with mRS ≥3 (75.23±10.50; $p=0.006$). Other demographic and vascular risk factors did not differ significantly between the groups ($p>0.05$), (Table 1). As a result of the comparison of laboratory parameters between the groups, hemoglobin, eosinophil, Ldl-cholesterol, total-cholesterol, and triglyceride values were significantly lower in the poor prognosis group (respectively; $p\leq0.001$, $p=0.01$, $p=0.01$, $p=0.02$, $p=0.01$). No differences were detected between the groups in terms of other laboratory parameters (Table 2).

ROC (Receiver Operator Characteristic Curve) analysis was performed to determine the cut-off point of hemoglobin, eosinophil, Ldl-cholesterol, total-cholesterol, and triglyceride to predict poor prognosis. As a result of ROC analysis, the area under the curve of hemoglobin, eosinophil, Ldl-cholesterol, total-cholesterol, and triglyceride was significantly higher (Figure 1). Hemoglobin (mg/dl) had the highest area under the curve with a cut-off value of 13.35. [(AUC: 0.710 95% CI:0.60-0.81); Sensitivity = 67.6%, Specificity = 67.9%, $p=0.001$]. The cut-off value for eosinophils (103/µl) was 0.12 (103/µl) [(AUC: 0.646 95% CI:0.53-0.76); Sensitivity = 64.9%, Specificity = 57.1%, $p=0.01$]. The cut-off value for Ldl-Cholesterol was 124.5 mg/dl [(AUC: 0.64195% CI: (0.52-0.76); Sensitivity = 64.9%, Specificity = 64.3%, p = 0, 02], the cut-off value for total-cholesterol was 179.5 mg/dl [(AUC: 0.64495% CI: (0.52-0.76); Sensitivity = 62.2.9%, Specificity = 69.6%. , $p=0.01$], the cut-off value for triglyceride was 121.5 mg/dl [(AUC: 0.64495% CI: (0.53-0.75); Sensitivity = 56.8%, Specificity = 58%, 9, $p=0.01$], (Table 3).

Table 1.

Comparison of demographic, clinical characteristics and vascular risk factors between groups

	Total (n=94)	**mRS <3 (n=56,%59,4)**	**mRS ≥3 (n=38,%40,4)**	**Test statistics**	***P***
Age (year)	71,18± 11,92	68,42±12,12	75,23±10,50	**-**2,81	**0,006**[a]
Gender, n (%)					
• Male • Female	47 (50) 47 (50)	30 (53,6) 26 (46,4)	17 (44,7) 21 (55,3	0,39	0,52[b]
Smoking, n (%)	22 (23,4)	15 (26,8)	7 (18,4)	0,47	0,48[b]
Antiplatelets, n (%)	39 (41,50)	19 (33,9)	20 (52,6)	2,5	0,11[b]
Statin, n (%)	10 (10,60)	5 (8,9)	5 (13,2)	-	0,51[c]
HT, n (%)	58 (61,70)	26 (46,4)	32 (84,2)	12,12	**<0,001**[b]
DM, n (%)	38 (40,40)	20 (35,7)	18 (47,4)	0,83	0,36[b]
HL, n(%)	13 (13,80)	7 (12,5)	6 (15,8)	0,02	0,88[b]
HF, n (%)	11 (11,70)	3 (5,4)	8 (21,1)	**-**	**0,04**[c]
CAD, n (%)	28 (29,80)	13 (23,20)	15 (39,5)	2,13	0,14[b]
AF, n (%)	34 (36,20)	15 (26,8)	19 (50)	4,32	**0,03**[b]
Infarct Volume (cm^3)	27,94 (0,04:356,48)	1,37 (0,04:66,47)/38,29	11,22 (0,18:356,48)/61,07	Z= -3,97	**<0,001**[d]
NIHSS_Initial	4 (1:25)	2 (1:20)/32,47	11 (2:25)/69,64	Z= -6,52	<0,001[d]

AF: Atrial Fibrillation, DM: Diabetes Mellitus, HL: Hyperlipidemia, HT: Hypertension, CAD: Coronary Artery Disease, HF: Heart Failure, NIHSS: The National Institutes of Health Stroke Scale, mRS: Modified Rankin Scale

mean ± standard deviation, median (minimum: maximum)/mean Rank and number (%)

a: t-Test for independent paired samples, b: Continuity correction, c: Fisher's Exact Chi-Square Test, d: Mann Whitney U Test

Table 2.

Comparison of laboratory parameters between groups

	Total (n=94)	mRS <3 (n=56)	mRS ≥3 (n=38)	Test statistics	*p*
Hemoglobin (g/dL)	13,32±2,07	13,97±1,75	12,35±2,13	t=4,01	**<0,001**[a]
WBC (*10³/µl)	8,45±2,27	8,38±2,12	8,53±2,49	Z=-0,29	0,76[a]
Eosinophil, (*10³/µl)	0,12 (0,01:0,55)	0,16 (0,01:0,55)/52,96	0,10 (0,01:0,47)/39,46	Z= -2,35	**0,01**[b]
Lymphocyte, (*10³/µl)	2,02 (0,21:5,70)	2,21 (0,64:5,70)/52,07	1,84 (0,21:5,46)/40,76	Z= -1,97	0,05[b]
ELR	0,06 (0:0,37)	0,07 (0:0,37)/51,47	0,04 (0:0,29)/41,64	Z=-1,71	0,08[b]
Neutrophil, (*10³/µl)	5,52 (1,85:13,08)	5,31 (1,85:11,18)/45,89	5,45 (1,96:13,08)/49,87	Z=-0,69	0,48[b]
Platelet, (*10³/µl)	251,34±76,33	247,10±68,60	257,57±87,07	t=-0,65	0,51[a]
PLR	107,71 (36,33:966,67)	101,24 (36,33:323,44)/43,79	110,40 (59,52:966,67)/52,96	Z=-1,59	0,11[b]
MPV, (*10³/µl)	9,57±1,10	9,71±1,09	9,37±1,07	1,48	0,14[a]
Hdl-Cholesterol, mg/dl	40,69±9	42,03±8,87	38,64±9,16	1,78	0,07[a]
Ldl-Cholesterol, mg/dl	125,33±39,39	133,10±37,83	113,56±39,28	2,40	**0,01**[a]
Total Cholesterol, mg/dl	190,60±51,01	200,07±51,75	176,27±46,98	2,35	**0,02**[a]
Triglyceride, mg/dl,	124(13:431)	133,00 (43:431)/52,32	115,00 (13:234)/38,95	Z=-2,33	**0,01**[b]
TC/HDL	4,77±1,20	4,85±1,18	4,66±1,24	0,70	0,48[a]
TG/HDL	3,35 (0,28:11,65)	3,47(0,84:11,65)/49,38	2,97(0,28:5,68)/43,41	1,60	0,08[a]

ELR: Eosinophil/Lymphocyte Ratio, MPV: Mean Platelet Volume, Hdl: High-density lipoprotein, Ldl: Low-density lipoprotein, PLR: Platelet/Lymphocyte Ratio, TC: Total Cholesterol, TG: Triglyceride

median (minimum: maximum)/mean Rank and mean ± standard deviation

a: t-Test for independent paired samples, b: Mann Whitney U Test

Table 3.

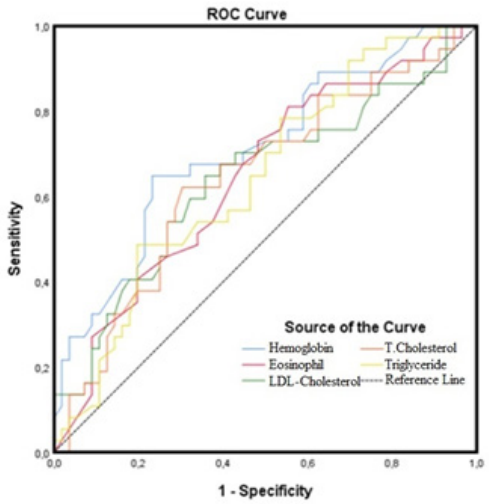
Area under curve (AUC), Sensitivity and Specificity

	AUC (%95 CI)	Cut off	Sensitivity	Specificity	P
Hemoglobin, (g/dl)	0,710 (0,60-0,81)	≤13,35	0,676	0,679	0,001
Eosinophil, (*103/µl)	0,646 (0,53-0,76)	≤0,12	0,649	0,571	0,01
Ldl-Cholesterol, mg/dl	0,641 (0,52-0,76)	≤124,5	0,649	0,643	0,02
Total Cholesterol, mg/dl	0,644 (0,52-0,76)	≤179,5	0,622	0,696	0,01
Triglyceride, mg/dl	0,644 (0,53-0,75)	≤121,5	0,568	0,589	0,01

Ldl: Low-density lipoprotein, AUC: Area under curve, CI: Confidence Interval

Figure 1.

ROC curve showing the predictive value of routine laboratory parameters for poor prognosis



Variables were included in the univariate and multivariate logistic regression model to identify risk factors for predicting poor prognosis. The results of univariate analyses and multivariate analyses are presented in Table 4, and the risk factors that are thought to affect poor prognosis are stated in the table. As a result of the analysis, it was seen that the multivariate logistic regression model was compatible with the data (Hosmer and Lemeshow test p=0.66) and the resulting logistic regression model was significant (p<0.001). As a result of the analysis, it was determined that the NIHSS score was 1.34 times higher than the risk of mRS ≥3 in the good prognosis group. In the multivariate logistic regression model, only the NIHSS score was independently associated with the degree of disability (p=0.001), (Table 4).

In the correlation analysis, it was determined that there was a significant negative relationship between laboratory values such as hemoglobin level (rs= -0.26; p=0.011), eosinophil level (rs= -0.24; p=0.021), Ldl-Cholesterol (rs= -0.28; p=0.006), and total-cholesterol levels (rs = -0.27; p = 0.008) and infarct volume. It was determined that there was a significant negative relationship between the laboratory parameters hemoglobin (rs= -0.23; p=0.02) and Ldl-cholesterol (rs= -0.21; p=0.04) and the NIHSS score (Table 5). No significant relationship was detected between the other parameters listed in Table 5 and infarct volume and NIHSS (p>0.05).

Table 4.

Analysis of parameters affecting clinical outcome using logistic regression model

	Univariate Logistic Regression Model		Multivariate Logistic Regression Model (Enter)	
	OR (%95CI)	***p***	**OR (%95CI)**	***p***
Age (year)	1,05 (1,01:1,09)	**0,008**	1,02 (0,95:1,09)	0,47
HT	6,15 (2,22:17,03)	**<0,001**	3,58 (0,77:16,45)	0,10
HF	4,71 (1,16:19,11)	**0,03**	1,10 (0,65:18,70)	0,94
AF	2,73 (1,14:6,51)	**0,02**	0,80 (0,18-3,41)	0,76
Infarct Volume (cm3)	1,05 (1,01:1,08)	**0,006**	1,02 (0,99:1,05)	0,19
NIHSS_Initial	1,41 (1,21:1,64)	**<0,001**	1,34 (1,12:1,60)	**0,001**
Hemoglobin (g/dl)	0,64 (0,49:0,82)	**0,001**	0,70 (0,44:1,11)	0,13
Eosinophil , (*103/µl)	0,01 (0,001:0,55)	**0,02**	0,03 (0,01-15,05)	0,27
Ldl-Cholesterol , mg/dl	0,98 (0,97:0,9)	**0,02**	1.00 (0,95:1,04)	0,85
Total Cholesterol , mg/dl	0,99 (0,98:0,99)	**0,03**	0,99 (0,96:1,04)	0,80
Triglyceride , mg/dl,	1 (0,98:0,99)	**0,02**	0,99 (0,97:1,01)	0,54
Constant			1,27	0,96

AF: Atrial Fibrillation, HT: Hypertension, HF: Heart Failure, NIHSS: The National Institutes of Health Stroke Scale, OR: Odds ratio, CI: Confidence Interval, Cox&Snell R2=0,50; Nagelkerke R2=0,68; Hosmer and Lemeshow ChiSquare=5,86

Table 5.

Relationship of laboratory parameters with infarct volume and NIHSS

	Infarct Volume	p	NIHSS	p
Monocyte (*103/µl)	0,14	0,18	0,06	0,57
Hemoglobin (g/dL)	-0,26	**0,01**	-0,23	**0,02**
WBC (*103/µl)	0,14	0,194	-0,10	0,33
Eosinophil, (*103/µl)	-0,24	**0,02**	-0,14	0,17
Lymphocyte , (*103/µl)	-0,07	0,50	-0,15	0,14
ELR	-0,17	0,10	-0,10	0,30
Neutrophil, (*103/µl)	0,15	0,13	-0,07	0,45
Platelet, (*103/µl)	0,01	0,89	-0,17	0,09
PLR	0,09	0,36	0,01	0,91
MPV, (*103/µl)	-0,09	0,39	-0,08	0,42
Hdl-Cholesterol, mg/dl	-0,12	0,26	-0,15	0,15
Ldl-Cholesterol, mg/dl	-0,28	**0,006**	-0,21	**0,04**
Total Cholesterol, mg/dl	-0,27	**0,008**	-0,19	0,06
Triglyceride, mg/dl	-0,15	0,162	-0,15	0,14
TC/HDL	-0,18	0,07	-0,08	0,43
TG/HDL	-0,06	0,52	-0,05	0,61

rs: Spearman Correlation Coefficient

ELR: Eosinophil/Lymphocyte Ratio, WBC: White Blood Cells, MPV: Mean Platelet Volume, Hdl: High-density lipoprotein, Ldl: Low-density lipoprotein, PLR: Platelet/Lymphocyte Ratio, TC: Total Cholesterol, TG: Triglyceride, NIHSS: The National Institutes of Health Stroke Scale

4. DISCUSSION

In our study, laboratory parameters; hemoglobin, eosinophil, Ldl-cholesterol, total-cholesterol, and triglyceride values were found to be low in the poor prognosis group. It is vital to identify risk factors affecting prognosis after stroke and to implement treatments to reduce the incidence of recurrent ischemic events. Some blood biomarkers can guide etiology, therapeutic approach, follow-up, and functional prognosis in acute ischemic stroke patients.[8] Many studies have been conducted on the effects of changes in hemogram and biochemistry parameters as a result of hypercortisolism and sympathetic hyperactivity resulting from the acute stress reaction associated with acute ischemic stroke on stroke prognosis. As a result of the studies conducted in this context, although the increase in the neutrophil/lymphocyte ratio and eosinopenia are among the poor prognostic factors, the reason for the relationship between biomarkers and prognosis is not fully known. [9-11] Similar to the literature, eosinopenia was detected in the poor prognosis group in our study. The relationship between hemoglobin level and post-stroke outcomes is contradictory. Some studies have revealed that low hemoglobin value at admission is associated with mortality and large infarct volume in stroke patients. This is thought to be caused by low hemoglobin levels that may reduce oxygen transport to ischemic penumbral regions.[12,13] However, in the study conducted by Zhang R. et al., it was reported that both low and high hemoglobin levels at the time of admission were associated with poor prognosis after AIS.[14] In another study investigating the factors affecting mortality, it was observed that hemoglobin and hematocrit levels were low and NIHSS scores were high in the poor prognosis group.[15] In our study, hemoglobin levels were found to be low in the poor prognosis group. It also showed a significant inverse correlation with both infarct volume and admission NIHSS score. It is thought that there is a decrease in oxygen-carrying capacity as a result of low hemoglobin levels.

İçme et al. showed that mean platelet volume (MPV) may be an important indicator of prognosis in AIS.[16] However, similar to our results, other studies[17,18] have reported that MPV does not have any prognostic significance in ischemic stroke. Additionally, similar to our study, it has been shown that leukocyte, neutrophil, lymphocyte, and platelet counts do not have prognostic significance. [16,19]

It has been reported that cholesterol is necessary for normal membrane function in the vascular system and that adequate cholesterol levels may be important for maintaining the integrity of the vessels and their resistance to tearing. [20] Hypercholesterolemia is a well-established risk factor for cardiovascular morbidity and mortality. However, the relationship between ischemic stroke and lipid profile is complex and studies contain paradoxical results. [21-24] Hyperlipidemia causes atherosclerosis as a result of lipid accumulation in the intima layer of the vessels, and atherosclerosis also creates a basis for stroke. [25,26] It is thought that the inverse correlation between acute ischemic stroke prognosis and LDL-cholesterol and triglyceride levels observed in some studies is due to lipid disorders causing small vessel strokes.[21-23] In our study, total-cholesterol, Ldl-cholesterol, and triglyceride values were significantly lower in the poor prognosis group, and this was consistent with studies. Also, it has been found that triglyceride and total cholesterol levels in stroke patients on admission may be a predictor of in-hospital mortality. [24] Han et al.'s study revealed a nonlinear relationship and a threshold value between the TG/HDL-c ratio and 3-month adverse outcomes in patients with AIS. [27] When the TG/HDL-c ratio is below 3.51, the prognosis worsens as the TG/

HDL-c ratio decreases. When the TG/HDL-c ratio is above 3.51, the prognosis worsens as the TG/HDL-c ratio increases. [27] In our study, the TG/HDL-c ratio was evaluated below the threshold value and was consistent with these results.

Although direct evidence of the relationship between eosinophils and thrombosis cannot be obtained by thrombus analysis in patients with acute ischemic stroke, histopathological findings suggest that eosinophils may play an important role in thrombus formation.[11] Wang et al. showed that there was a significant inverse correlation between NIHSS and WBC (White blood cells), eosinophils, eosinophil percentage, and LDL-cholesterol.[11] In our study, it was observed that only hemoglobin and LDL-cholesterol had a negative significant relationship with the NIHSS score, and did not show a significant correlation with other parameters. The literature is examined; it was thought that factors such as the timing of samples taken from patients, calculation of differences by seeing control values, and the number of patients may cause the difference in results.

In multivariate regression analysis, it was determined that laboratory parameters were not significant and admission NIHSS score was the only predictor of poor prognosis.

Our study has some limitations. First, the study reflects the results of a single center after a retrospective review, and therefore generalizations cannot be made. Secondly, it was made with values obtained as a result of a measurement in a limited number of cases. To investigate the prognostic value of hematological and biochemical parameters in stroke, studies with a prospective design and larger sample size will provide more accurate results. Stronger statistical results will be obtained with more participants.

NIHSS is an independent factor in predicting stroke outcomes. In this study, a relationship was found between routine laboratory parameters hemoglobin level, eosinophil level, LDL and total cholesterol levels, and infarct volume. Additionally, it was determined that there was a significant negative correlation between hemoglobin and LDL-cholesterol and NIHSS scores.

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Disclosure of interest

The authors declare that there is no conflict of interest.

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Ethics Committee Approval

The study protocol was approved by the local ethics of Kutahya Health Sciences University (2024/06-27), and approval and local institutional approvals were obtained for the study.

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Research Article/ Araştırma Makalesi

Diyabetli Hastalarda Diyabetik Periferal Nöropati ile İlişkili Faktörlerin Değerlendirilmesi

Evaluation of Factors Associated with Diabetic Peripheral Neuropathy in Patients with Diabetes

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Giriş: Diyabetik periferal nöropati, diyabetin uzun sürede görülen ve göz ardı edilen önemli bir komplikasyonudur. Diyabetik polinöropatinin (DPN) varlığı, tekrarlayan alt ekstremite enfeksiyonları, ülserasyonlar ve takip eden ampütasyonlar başta olmak üzere ciddi morbiditelere yol açar ve erken tanınması önem taşımaktadır. Çalışmamızda DPN ile ilişkili faktörlerin irdelenmesi ve nöropatide hızlı tanı testiyle erken ve hızlı teşhisin önemi vurgulanmaya çalışılmıştır.

Materyal Metod: Diyabetes Mellitus (DM) tanılı hastalara Diyabetik Nöropatik Ağrı Anketi (Douler Neuropathique 4 Questions DN-4) yapıldı. Ayrıca dokunma hipoestezisi iğne hipoestezizi ve extremitede dokunma ile ağrı olup olmadığı muayene edildi. Hastaların demografik özellikleri sorgulanıp kayıt edildi. Rutin labaratuar sonuçlarından elde edilen veriler kayıt altına alındı.

Bulgular: Çalışmaya 60 kadın (%57.7) 44 (%42.3) erkek hasta alındı. Çalışmaya alınan hastaların 56'sında (%53.8) Diyabetik Nöropati saptandı. DN-4 skoru ile HbA1c ve Diyabet yıl arasında yüksek korelasyon saptandı (sırasıyla r=0.791, p< 0.001, r =0.692, p< 0.001). DN-4 skoru LDL kolesterol trigliserid düzeyi arasında zayıf korelasyon saptandı (sırasıyla r= 0.124, p=0.364, r=0.183, p=0.176). DN-4 Skoruna göre Diyabetik Nöropati olan hastalar sınıflandırıldığında cinsiyete bağlı her iki grup arasında farklılık saptanmadı (p=0.383). Çalışmamızda 62 yaş DPN için kesim noktası değeri olarak saptandı (p<0.001). Buna göre hasta yaşının 62 yıl üstü olması DPN için kesim noktası değeridir. Bu ileri yaş ile DPN riskininin arttığını göstermektedir. Ayrıca HbA1c 7,6 üzeri olması DPN tanısı için ve 6 yıl ve üzeri diyabet geçmişi olması DPN gelişmesi için anlamlı olarak saptandı (p<0.001).

Sonuç: Çalışmamıza göre yüksek HbA1c, ileri yaş ve diyabet süresinin artmasıyla DPN riski artış göstermektedir. Çalışmamız tarama testlerinin poliklinik şartlarında yapılabilirliğini göstermesi ve farkındalık oluşturması açısından önemlidir.

Anahtar Kelimeler: Diyabetes mellitus, Diyabetik periferal nöropati, HbA1c, Diyabetik nöropatik ağrı anketi

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Introduction: Diabetic peripheral neuropathy is an important long-term and ignored complication of diabetes. The presence of diabetic polyneuropathy (DPN) causes serious morbidities, especially recurrent lower extremity infections, ulcerations and subsequent amputations, and early diagnosis is important. Our study aimed to examine the factors associated with DPN and to emphasize that morbidity can be prevented with early and rapid diagnosis of neuropathy.

Material Method: Diabetic Neuropathic Pain Questionnaire (Douler Neuropathic 4 Questions DN-4) was administered to patients diagnosed with Diabetes Mellitus (DM). Additionally, touch hypoesthesia, needle hypoesthesia, and pain to touch in the extremity were examined. The demographic characteristics of the patients were questioned and recorded. Data obtained from routine laboratory results were recorded.

Results: 60 female (57.7%) and 44 (42.3%) male patients were included in the study. Diabetic Neuropathy was detected in 56 (53.8%) of the patients included in the study. A high correlation was detected between DN-4 score and HbA1c and Diabetes Year (r=0.791, p< 0.001, r =0.692, p< 0.001 respectively). A weak correlation was detected between DN-4 score and LDL cholesterol triglyceride level (r= 0.124, p=0.364, r=0.183, p=0.176, respectively). When patients with Diabetic Neuropathy were classified according to the DN-4 Score, no difference was found between the two groups based on gender (p = 0.383). In our study, 62 years of age was determined as the cut-off point for DPN (p<0.001). Accordingly, patient age over 62 years is the cut-off point for DPN. This shows that the risk of DPN increases with advanced age. In addition, HbA1c over 7.6 was found to be significant for the diagnosis of DPN and a history of diabetes of 6 years or more was found to be significant for the development of DPN (p<0.001).

Conclusion: According to our study, the risk of DPN increases with high HbA1c, advanced age, and increased duration of diabetes. Our study is important in terms of demonstrating the feasibility of screening tests in outpatient clinics and raising awareness.

Keywords: Diabetes mellitus, Diabetic peripheral neuropathy, HbA1c, Diabetic neuropathic pain questionnaire

EXTENDED ABSTRACT

Introduction

Diabetic peripheral neuropathy (DPN) is an important complication of diabetes that is seen in the long term and is ignored (1). In patients with Diabetes Mellitus (DM), long-term hyperglycemia causes damage to peripheral nerves. According to the symptoms and findings of DPN, it presents with different clinical presentations, the most common being distal symmetric polyneuropathy (2). The duration and severity of hyperglycemia are the most important risk factors for the development of diabetic neuropathy (3). The presence of DPN leads to serious morbidities, primarily recurrent lower extremity infections, ulcerations and subsequent amputations, so early diagnosis is important (4). Our study aims to examine the factors associated with DPN and to emphasize that neuropathy can be diagnosed early and rapidly with the Diabetic Neuropathic Pain Questionnaire (Douler Neuropathique 4 Questions DN-4), which can be performed in outpatient clinics.

Material Method

Approval was obtained from the Harran University ethics committee for the study (session dated 18.03.2024, decision numbered HRÜ/24.02.2012). Patients previously diagnosed with DM and newly diagnosed DM were included in the study between April 1, 2024 and July 1, 2024. Pregnant patients under the age of 18, patients with malignancy, and patients receiving active chemotherapy were not included in the study. The 4-question Diabetic Neuropathic Pain Questionnaire (Douler Neuropathique 4 Questions DN-4) was administered to the patients. The patients were

questioned about the number of years they had DM, their comorbid diseases, the treatment agents they used, and their demographic characteristics were recorded. Routine laboratory results of the patients were recorded as follows; Urea, Creatine, Electrolytes, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), HbA1c, LDL Cholesterol, Triglyceride, Magnesium (Mg) level, Vitamin D level, and proteinuria level.

Statistical Analysis

Descriptive statistics were performed to provide information about the general characteristics of the study groups. Data for quantitative variables were defined using mean and standard deviation (x ± ss); data for qualitative variables were defined using number (n) and percentage (%). Levene test was used to check whether the data for continuous variables were normally distributed. Ready-made statistical software was used in the calculations. (IBM SPSS Statistics 22, SPSS inc., an IBM Co., Somers, NY)

Results

The study included 60 female (57.7%) and 44 (42.3%) male patients. While 48 (46.2%) of the patients included in the study did not have DPN, 56 (53.8%) patients were diagnosed with DPN. When patients with and without Diabetic Neuropathy were divided into two groups, there was a difference between Diabetes years, DN-4 Score HbA1c level, Spot Urine Protein/Creatine ratio, Mg level (p value for each $p<0.001$). A weak correlation was found between DN-4 score and LDL cholesterol Triglyceride level ($r=0.124$, $p=0.364$, $r=0.183$, $p=0.176$, respectively). A weak inverse correlation was found between DN-4 score and Mg, vitamin D and B12 level ($r= -0.136$ $p=0.318$, $r= -0.232$ $p=0.086$, $r= -0.016$ $p=0.909$, respectively). In our study, a significant effect of HbA1c, one of the independent variables, on the dependent variable DN-4 Score result was calculated. Accordingly, for each unit increase in the HbA1c value, the probability of diabetic neuropathy increases by 3.513 units.

Discussion

DPN is the most common neurological complication of diabetes and is a significant cause of morbidity (5). DPN leads to a gradual loss of nerve fiber integrity, and symptoms begin distally and symmetrically in the toes and feet. It causes sensory loss and the risk of foot ulcers and amputation, as well as painful symptoms that limit function and reduce quality of life in approximately 15 to 20 percent of patients. Type 2 diabetes should be screened for DPN at the time of diagnosis and within five years after type 1 diabetes diagnosis (6,7). Screening tests used to diagnose DPN do not require electrodiagnostic evaluations with nerve conduction studies or quantitative sensory tests, but these methods can also be used when clinical features are atypical (8).Numerous clinical studies have shown that there are several risk factors associated with the risk of developing DPN. These include longer duration of DM, higher HbA1c levels, hypertension, obesity, dyslipidemia, smoking, chronic alcohol use, and old age (9,10). Advanced age and duration and severity of hyperglycemia are the main risk factors for the development of diabetic neuropathy in patients with both type 1 and type 2 diabetes (9). When the group with Diabetic Neuropathy was evaluated in our study, the age was determined as 60.8±10.05 years. A high correlation was found between the DN-4 score and HbA1c and years of diabetes in patients with Diabetic Neuropathy ($r=0.791$, $r=0.692$, respectively). In addition, in our study, being over 62 years of age was determined as the cut-off point value for DPN, and an HbA1c of 7.6 or more was found to be significant for the diagnosis of DPN. In the Verona Diabetic Foot Imaging Program study, the mean HbA1c in 1100 patients with DPN was 7.54, and in a cross-sectional study conducted

in 60 centers in China with 3359 type 2 diabetic patients, the mean HbA1c in the DPN group was 8.75% (11). In our study, the mean HbA1c in the Diabetic Neuropathy group was 9.65±2.28.

Conclusion

According to our study, the risk of DPN increases with high HbA1c, advanced age and increasing duration of diabetes. The probability of diabetic neuropathy increases by 3.513 units for each unit increase in HbA1c value. Our study is important in that the DN4 questionnaire, one of the rapid questionnaires used in the diagnosis of DPN, saves significant time in diagnosing the disease and shows that it can be performed in outpatient clinic conditions.

GİRİŞ

Diyabetik periferal nöropati (DPN), diyabetin uzun sürede görülen ve göz ardı edilen önemli bir komplikasyonudur (1). Diyabetli Mellituslu (DM) olgularda uzun süreli hiperglisemi periferal sinirlerin hasarlanmasına sebep olur. DPN semptom ve bulgularına göre, en sık distal simetrik polinöropati olmak üzere, farklı klinik tablolarla karşımıza çıkar (2). Hipergliseminin süresi ve ağırlığı diyabetik nöropati gelişiminin en önemli risk faktörüdür (3). DPN'nin varlığı tekrarlayan alt ekstremite infeksiyonları, ülserasyonlar ve takip eden ampütasyonlar başta olmak üzere ciddi morbiditelere yol açar bu yüzden erken tanınması önem taşımaktadır (4). DPN'nin saptanmasında altın bir standart yoktur ve tanı için semptomların ve fizik muayene bulgularının birlikte değerlendirilmesi gerekir. DPN'si olan hastaların yaklaşık yarısında semptom olmayabilir, ama bu hastaların fizik muayenesinde hafiften orta şiddete kadar değişen duysal his kaybı görülür (5,6). Diyabet hastalarında ekstremite kayıpları ile artmış morbidite ve maluliyetin en sık nedenlerinden biri olduğu bilinen DPN diyabetli hastaların rutin değerlendirmesinde sıklıkla gözardı edilmektedir. Sıklıkla hastaların şikayetlerini ifade etmesi ile tedavi başlanmakta veya hastalar ileri değerlendirme amaçlı kliniğe yönlendirildiğinde tedavi başlanmaktadır. Bu durum tanının gecikmesine hastaların diyabetik ayak gibi komplikasyonlarla kliniklerle başvurmasına yol açmaktadır.

Çalışmamızda DPN ile ilişkili faktörlerin irdelenmesi ve poliklinik şartlarında yapılabilen Diyabetik Nöropatik Ağrı Anketi (Douler Neuropathique 4 Questions DN-4) ile nöropatinin erken ve hızlı teşhis edilebileceği vurgulanması hedeflenmektedir.

MATERYAL METOD

Çalışma için Şanlıurfa Mehmet Akif İnan Eğitim ve Araştırma Hastanesi Tıpta Uzmanlık Etik Kurulundan (TUEK) onay alındıktan sonra Harran Üniversitesi etik kuruldan onay alınmıştır (18.03.2024 tarihli oturum HRÜ/24.02.2012 nolu karar). 1 Nisan 2024 ve 1 Temmuz 2024 tarihleri arasında daha önceden DM tanısı olan ve yeni tanı DM olan hastalar çalışmaya alındı. 18 yaş altı gebe, malignitesi olan ve aktif kemoterapi alan hastalar çalışmaya alınmadı. Hastalara çalışma hakkında bilgi verildikten sonra onam belgesi imzalatıldı. Şanlıurfa Mehmet Akif İnan Eğitim ve Araştırma Hastanesi Dahiliye polikliniğine başvuran hastalardan DPN düşünülen hastalara 4 soruluk Diyabetik Nöropatik Ağrı Anketi (Douler Neuropathique 4 Questions DN-4) yapıldı. Hastalara ağrı ile ilgili; yanma hissi, ağrı ve elektrik şoku olup olmadığı ve ilişkili olduğu durum; karıncalanma, çivi-iğne batması, uyuşma, kaşınma durumu soruldu. Belirtilen her semptomun var olması 1 puan, semptom olmaması 0 puan olarak puanlandı. Ayrıca dokunma hipoestezisi iğne hipoestezizi ve extremitede dokunma ile ağrı olup olmadığı muayene edildi. Muyanede pozitif her bulgu için 1 puan verildi. Toplam skor 4'ün üstü olması DPN olduğunu göstermektedir. Hastalara kaç yıldır DM oldukları komorbid hastalıkları

kullandıkları tedavi ajanları demografik özellikleri sorgulanıp kayıt edildi. Hastaların rutin labaratuar sonuçlarından; Üre, Kreatin, Elektrolitler, Aspartat Aminotransferaz(AST), Alanin Aminotransferaz(ALT), HbA1c, LDL Kolesterol, Trigliserid, Magnezyum(Mg) düzeyi, D vitamin düzeyi, proteinüri düzeyi kayıt altına alındı. DN-4 anketi Bouhassira ve ark. 2005'de yaptığı bir çalışmayla ortaya konuldu, kullanıma açık ve DPN'nin taramasında kullanılabilen bir ankettir (7).

İSTATİSTİKSEL ANALİZ

Çalışma gruplarının genel özellikleri hakkında bilgi vermek amacı ile tanımlayıcı istatistikler yapılmıştır. Nicel değişkenlere ait veriler ortalama ve standart sapma (x ± ss); nitel değişkenler ait veriler sayı (n) ve yüzde (%) kullanılarak tanımlandı. Sürekli değişkenlere ait verilerin normal dağılıma uyup uymadığını kontrol etmek için Levene testi kullanıldı. Bağımsız gruplar için nicel değişkenlere ilişkin gruplar arası farklar Bağımsız Örneklem T Testi ile; nitel gruplar arası farklar ise Ki-Kare Testi ile değerlendirilmiştir. Değişkenler arasındaki ilişkilerin incelenmesi için Pearson Korelasyon Analizi ve Lojistik Regresyon Analizi uygulanmıştır. Değişkenlerin kesim değerlerinin belirlenmesi için ise ROC (Receiver Operating Characteristics) eğrisi analizi uygulandı ve ayrıca Roc eğrisi altında kalan alan (AUC) değerlendirildi. P değerleri 0.05'den küçük hesaplandığında istatistiksel olarak anlamlı kabul edilmiştir. Bağımlı Değişken: DN4 Skor (Dikotom) Bağımsız Değişkenler: yaş, diyabet süresi, Hbac1 olarak belirlendi. Analiz sonucuna göre modelin iyi uyum gösterip göstermediğine ilişkin Hosmer and Lemeshow Testi uygulanmıştır. Regresyon analizinde Diyabetik Nöropati ile yaş için en anlamlı olabilecek kesim noktasını saptamak amaçlı ROC analizi yapıldı. Hesaplamalarda hazır istatistik yazılımı kullanılmıştır. (IBM SPSS Statistics 22, SPSS inc., an IBM Co., Somers, NY)

BULGULAR

Çalışmaya 60 kadın(%57.7) ve 44(%42.3) erkek hasta alındı. Çalışmaya alınan hastaların 48'inde(%46.2) DPN yokken, 56(%53.8) hastada DPN saptandı. Çalışmaya alınan hastalarla ile ilgili nitel ve nicel değişkenler tabloda belirtilmiştir (Tablo 1).

DN-4 Skoruna göre Diyabetik Nöropati olan hastalar sınıflandırıldığında cinsiyete bağlı her iki grup arasında farklılık saptanmadı (p=0.383) (Tablo 2).

Diyabetik Nöropati olan hastalarla olmayan hastalar iki gruba ayrıldığında Diyabet yıl, DN-4 Skor HbA1c düzeyi, Spot İdrar Protein/Kreatin oranı, Mg düzeyi arasında fark bulundu (p değeri her biri için p<0.001). Her iki grup arasında yaş, kreatin, LDL kolesterol, Trigliserid düzeyi, D vitamin düzeyi, B12 vitamin düzeyi, Folat düzeyi, Ferritin, ALT ve AST düzeyleri arasında 2 grupta fark bulunmamıştır.

DN-4 skoru ile HbA1c ve Diyabet Yıl arasında yüksek korelasyon saptandı (sırasıyla r=0.791, p<0.001, r =0.692, p<0.001). DN-4 skoru LDL kolesterol Trigliserid düzeyi arasında zayıf korelasyon saptandı (sırasıyla r= 0.124, p=0.364, r=0.183, p=0.176). DN-4 skoru ile Mg, D vitamini ve B12 düzeyi arasında zayıf düzeyde ters korelasyon saptandı (sırasıyla r= -0.136 p=0.318, r= -0.232 p=0.086, r= -0.016 p=0.909) (Tablo 3).

Çalışmamızda bağımsız değişkenlerden HbA1c'nin bağımlı değişken DN-4 Skor sonucu üzerinde anlamlı bir etkisi hesaplanmıştır. Buna göre HbA1c değerinin her bir birim arttığında diyabetik nöropati olma ihtimali 3.513 birim artmaktadır (Tablo 4).

Analiz sonucuna göre modelin iyi uyum gösterip göstermediğine ilişkin Hosmer and Lemeshow

Testi uygulanmıştır. P değeri 0.411 olarak bulunup modelin uyumu iyidir. Modele ilişkin Seçicilik (Specifty) Oranı 87.5; Duyarlılık (Sensitivity) Oranı 82.1 olarak bulundu. Yine modele ilişkin bağımsız değişkenlerin bağımlı değişkeni açıklama oranını veren Nagelkerke R Square değeri 0.660 olarak hesaplandı. Yani bağımsız değişkenlerin bağımlı değişkene ait varyansın %66'sını açıklayabilmektedir. Çalışmamızda yaş için ROC eğrisi altında kalan alan 0.646 (%95 Düzeyinde Güven Sınırları: 0.546-0.737) (p=0.007). Çalışmamıza göre hasta yaşının 62 yıl üstü olması DPN için kesim noktası değeridir. Diyabet süresi için ROC eğrisi altında kalan alan 0.818 (%95 Düzeyinde Güven Sınırları:0.730-0.887) (p<0.001). Çalışmamıza göre 6 yıl üstü diyabet geçmişi diyabetik nöropati varlığı için kesim noktası değeridir. HbA1c için ROC eğrisi altında kalan alan 0.901 (%95 Düzeyinde Güven Sınırları: 0.827-0.951) (p<0.001). Diyabetik nöropati varlığı için HbA1c 7.6 üstü olması kesim noktası olarak bulunmuştur (Çizim 1).

Table 1.

Değişkenlere ilişkin dağılımlar (n=104)

Nitel Değişkenler			
		n	**%**
Cinsiyet	Kadın	60	57.7
	Erkek	44	42.3
DN-4 Skor	Diyabetik Nöröpati Yok	48	46.2
	Diyabetik Nöropati Var	56	53.8
Nicel Değişkenler			
		Ort±SS	**Min-Mak**
Yaş		58.61±9.94	27-78
Diyabet Yıl		5.77±3.91	1-17
DN-4 Skor		4.63±2.63	1-10
Kreatin (mg/dl)		0.81±0.29	0.36-2.3
HbA1c (%mmol/mol)		8.34±2.24	5-16
LDL kolesterol (mg/dl)		135.61±35.83	55-240
Trigliserid (mg/dl)		246.85±111.92	51-639
Spot İdrar Protein/Kreatin Oranı (mg/dl)		0.27±0.3	0.01-1.45
Magnezyum (mmol/L)		1.7±0.26	0.85-2.3
D Vitamini (ng/ml)		17.02±8.04	4-49
B12 Vitamini (ng/L)		379.14±147.58	120-850
Folat Düzeyi (ug/L)		10.34±4.53	1.6-25
Ferritin (ug/L)		101.14±131.87	3.4-1174
ALT (U/L)		28.64±17.97	6-116

DN-4: Douler Neuropathique 4 Questions
HbA1c: Glikozile Hemoglobin
ALT: Alanin Aminotransferaz

Tablo 2.

Nitel değişkenlerin gruplara göre dağılımı

		DN-4 Skor		p
		Diyabetik Nöröpati Yok	**Diyabetik Nöropati Var**	
Cinsiyet	Kadın	25(52.1)	35(62.5)	0.383
	Erkek	23(47.9)	21(37.5)	

DN-4: Douler Neuropathique 4 Questions

Tablo 3.

Diyabetik nöropatisi olan hastalarda DN-4 Skoru ile nicel değişkenlerin korelasyonu (n=56)

		HbA1c	Diyabet Yıl	Ldl	Tg	Mg	Devit	B12
DN-4 Skor	**r**	0.791	0.692	0.124	0.183	-0.136	-0.232	-0.016
	p	**<0.001***	**<0.001***	0.364	0.176	0.318	0.086	0.909

DN-4: Douler Neuropathique 4 Questions

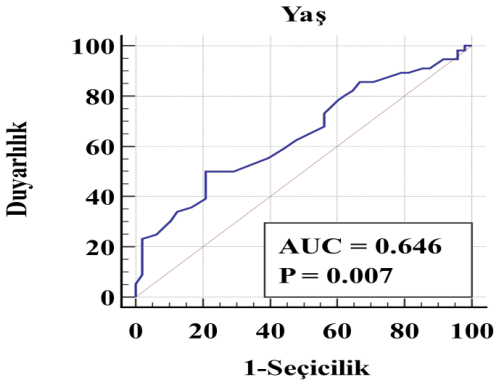
Tablo 4.

Lojistik regresyon analizi verilerine göre Diyabetik Nöropatiyi predikte eden parametreler

Modele Giren Bağımsız Değişkenler	**B**	**S.E.**	**Wald**	**df**	**p**	**Exp(B)**	**EXP(B) için %95 Güven Sınırları**	
							Alt	**Üst**
Yaş	0.049	0.033	2.214	1	0.137	1.050	.985	1.119
Diyabet Yıl	0.251	0.139	3.265	1	0.071	1.285	.979	1.686
HbA1c	1.256	0.361	12.080	1	**0.001***	3.513	1.730	7.135
Sabit	-13.565	3.254	17.382	1	<0.001	.000		

Çizim 1.

Diyabet hastalarında yaş için ROC analizi



TARTIŞMA

DPN diyabetin en sık görülen nörolojik komplikasyonudur ve önemli bir morbidite nedenidir (8). DPN sinir liflerinin bütünlüğünü kademeli olarak kaybolmasına yol açar ve semptomlar ayak parmaklarında ve ayaklarda distal ve simetrik olarak başlar. Duyusal kayıp ve ayak ülseri ve amputasyon riskine yol açmakla beraber hastaların yaklaşık yüzde 15 ila 20'sinde işlevi sınırlayan ve yaşam kalitesini azaltan ağrılı semptomlara neden olur. Tip 2 DM tanısı konulduğu anda ve tip 1 DM tanısından sonraki beş yıl içinde DPN açısından taranmalıdır (9,10).

DPN'yi teşhis etmek için kullanılan tarama testleri sinir iletim çalışmaları veya kantitatif duyu testleri ile elektrodiagnostik değerlendirmelerini gerektirmez ancak klinik özellikler atipik olduğunda bu yöntemler de kullanılabilir (11).

DPN'nin ana semptomları arasında uyuşukluk, denge kaybı, karıncalanma ve ağrı yer alır. Semptomlar ayak parmaklarında ve ayaklarda distalden başlar ve semptomlar genellikle geceleri daha kötüdür (12). Ancak bazı hastaların çok az şikayeti vardır. DPN olan hastaların yarısı da asemptomatik olabilir. Hastalığın ilerlemesiyle birlikte duyu kaybı artar ve yaklaşık olarak baldırın ortasına ulaştığında ellerde görülür. Bu kademeli ilerleme, tipik "çorap eldiven" duyu kaybına neden olur (11).

DPN'nin tanısı diyabetli bir hastadaki klinik bulgulara dayanmaktadır. Bunlar; özellikle simetrik distal duyu kaybı ve semptomların yokluğunda veya sadece ağrısız ayak ülseri varlığında muayenedeki tipik bulguların olmasıdır. Diyabetli hastalarda nispeten yaygın olan belirli polinöropati türleri dışlanmalıdır. Bunlar arasında B12 vitamini eksikliği, alkol kullanımı, kronik böbrek hastalığı, kemoterapi, kalıtsal nöropatiler, paraproteinemi ve kronik inflamatuar demiyelinizan polinöropati (KİDP) yer almaktadır (11). Çalışmamızda DN-4 skoru ile Mg düzeyi, D vitamini ve B12 arasında zayıf düzeyde ters korelasyon saptandı. Bu nutrisyonun nöropati üzerindeki etki edebileceği ve DPN şiddetinin nutrisyonel eksikliklerde artabileceğini göstermesi açısından anlamlıdır.

Çok sayıda klinik çalışmada DPN gelişme riskiyle ilişkilendirilen çeşitli risk faktörleri olduğu gösterilmiştir. Bunlar arasında DM'nin daha uzun sürmesi, daha yüksek HbA1c seviyeleri, hipertansiyon, obezite, dislipidemi, sigara kullanımı, kronik alkol kullanımı ve yaşlılık yer almaktadır (13,14). İleri yaş ve hipergliseminin süresi ve şiddeti, hem tip 1 hem de tip 2 DM'li hastalarda DPN'nin gelişmesinde ana risk faktörleridir (13). Çalışmamızda DPN olan grup değerlendirildiğinde yaş 60.8±10.05 yıl olarak saptandı. DPN olan hastalarda DN-4 skoru ile HbA1c ve Diyabet yılı arasında yüksek korelasyon saptandı (sırasıyla r=0.791, r =0.692). Ayrıca çalışmamızda 62 yaş üstü olması DPN için kesim noktası değeri olarak saptandı ve HbA1c 7,6 üzeri olması DPN tanısı için anlamlı olarak bulunmuştur.

Yapılan çalışmalarda DM olma süresi arttıkça DPN prevalansı artmaktadır. Tip 2 DM'li hastalarda

DPN seyrini değerlendiren Finlandiya'daki bir çalışmada; DPN tanısı hem klinik (ağrı ve parestezi) hem de elektrodiagnostik (sinir iletim hızı ve yanıt-genlik değerleri) kriterlere göre konuldu. Kesin veya olası polinöropatinin prevalansı, başlangıçta yüzde 8'den 10 yılda yüzde 42'ye artmıştır (15). Çalışmamızda ise 6 yıl ve üzeri DM geçmişi olması DPN gelişmesi için anlamlı bulunmuştur. Ayrıca DPN hastalarında DN-4 skoru ile Diyabet yılı arasında yüksek korelasyon saptandı (r =0.692).

Tip 2 diyabetli 6669 hastada yapılan dört çalışmanın meta-analizinde, gelişmiş glikoz kontrolü ile yıllık DPN riskinde azalma saptanmıştır (16). Çalışmamızda HbA1c için ROC eğrisi altında kalan alan 0.901 (%95 Düzeyinde Güven Sınırları: 0.827-0.951) (p<0.001). Buna göre HbA1c 7.6 değeri diyabetik nöropati varlığı için kesim noktası değeridir. Çalışmamızda HbA1c değerinin her bir birim arttığında diyabetik nöropati olma ihtimali 3.513 arttığı saptandı. Ayrıca DN-4 skoru ile HbA1c arasında yüksek korelasyon saptandı.

Verona Diyabetik Ayak Görüntüleme Programı çalışmasında takipli DPN saptanan 1100 hastada HbA1c ortalaması 7.54, Çin'de 60 merkezde takipli 3359 tip 2 diyabetli hasta ile gerçekleştirilen kesitsel çalışmada DPN olan grupta HbA1c ortalaması %8,75 saptanmıştır. (17). Çalışmamızda ise Diyabetik Nöropati olan grupda HbA1c ortalaması 9.65±2.28 olarak saptandı.

Yapılan bir çalışmada cinsiyet ile toplam nöropati puanı arasında anlamlı bir ilişki bulunamamıştır (18). Booya ve ark. yaptığı çalışmada erkek cinsiyet olması diyabetik hastalarda nöropatinin daha sık görüldüğünü bildirmişlerdir (19). Ancak Barbosa ve ark. ve Perkins ve ark. yaptıkları çalışmada DPN açısından cinsiyetler arasında fark olmadığını bildirmiştir (20). Çalışmamızda literatür ile benzer olarak DN-4 skoruna göre diyabetik nöropati olan ile olmayan grup arasında cinsiyete bağlı her iki grup arasında farklılık saptanmadı.

SONUÇ

Çalışmamıza göre yüksek HbA1c, ileri yaş ve diyabet süresisinin artmasıyla DPN riski artış göstermektedir. HbA1c değerinin her bir birim arttığında diyabetik nöropati olma ihtimali 3.513 birim artmaktadır. DPN diyabetli hastalarda sık görülen bir komplikasyon olmasına rağmen genelde geç teşhis edildiğinden tedavi zorlaşmaktadır. Bundan dolayı DPN'nin erken teşhisi morbiditenin önlenmesinde sağlık harcamalarının azalmasında önemlidir. Çalışmamız DPN tanısında kullanılan hızlı anketlerden DN4 anketinin hastalığın teşhis edilmesinde önemli zaman kazandırması ve poliklinik şartlarında yapılabilir olmasını göstermesi açısından önemlidir.

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Research Article

Determination of Learning Needs of Patients Undergoing Total Knee Replacement Surgery at Discharge

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Introduction: This study was planned to determine the learning needs of patients who underwent total knee replacement (TKR) surgery at discharge.

Materials and Methods: The research sample consisted of 60 patients aged 18 and over who had undergone total knee replacement surgery in the orthopedic service of a Training and Research Hospital and agreed to participate in the study. Patients were interviewed in the postoperative period using the Personal Data Form and the Patient Learning Needs Scale (PLNS).

Results: The average age of the patients who underwent surgery was 65.03±6.88 and the average BMI was 29.58±3.52. While the average length of hospital stay (days) was 5.30±1.69, 78.3% were women and 88.3% underwent spinal anesthesia. All patients and caregivers received discharge training on home care. The patient PLNS score is 168.90±32.34.It was observed that the highest importance level score among the patients' scale subgroups was treatment and complications.

Conclusions: The learning needs of the patients were found to be moderately important. It was determined that the importance levels of patient education needs were higher for those with spinal anesthesia, those with primary school education or higher, those who were single, and those whose income was less than their expenses. It was observed that the importance levels of the feelings about the situation and treatment complications sub-dimensions of the PLNS were higher in those who had not had surgery before than in those who had surgery.

Keywords: Care, Orthopedic nursing, Post-surgical, Total knee replacement

1. INTRODUCTION

Total knee arthroplasty (TKA) is a surgical intervention performed in patients who have difficulty in fulfilling the biomechanical activity of the knee and complain of pain that decreases the quality of life, mostly in female patients over 60 years of age. These patients mostly present to health centers with complaints of osteoarthritis.[1] This intervention, which has indications such as overweight, osteoarthritis, rheumatoid arthritis, gonarthrosis, advanced age, osteoporosis, pain in the knee and decreases the quality of life, is an effective and elective surgery that is successful with the right patient selection.[1-3] Patients are very concerned about the process and adaptation in the postoperative period, as they do not have enough information about the surgery and adaptation to the implant in the following time period. As a requirement of holistic care, patients should be supported in all aspects and their information needs about the postoperative process and adaptation should be identified and met. [4,5] Based on this, the study was planned to determine the learning needs at discharge in patients who underwent TKR surgery.

2. MATERIALS AND METHODS

The study population consisted of patients aged 18 years and over who underwent total knee replacement

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surgery between 01.08.2022-01.04.2024 in the Orthopedics Clinic of a Training and Research Hospital, and the sample consisted of 60 patients (47 females and 13 males) who agreed to participate in the study and met the research criteria. The number of patients planned to be included in the study was found to be at least 60 patients in case of low effect size (0.31), α: 0.05 and power: 80% by selecting t test for repeated measure comparison in G-Power 3.1.9.4 program.

Data Collection Tools

While collecting the data, 'Personal Data Form' and 'Patient Learning Needs Scale', which were created by the researchers by reviewing the relevant literature, were used.

Personal Data Form

The Personal Data Form consists of questions such as age, gender, education level, height-weight, marital status, employment status, any chronic disease status, presence of any allergy, previous surgery status, discharge training status, having a companion and the duration of the companion's stay in line with the relevant literature.[1-3]

Patient Learning Needs Scale (PLNS)

The Patient Learning Needs Scale (PLNS) was developed by Bubela et al. in 1990 for the first time to address the information needs of surgical patients based on the suggestions made by Lazarus and Folkman in 1987 for individuals to adapt to and cope with the new situation and to meet their information needs.[6] The validity and reliability of the scale in Turkey was performed by Çatal and Dicle (2008) and the Cronbach's alpha value was found to be 0.95.[7] In this study, the Cronbach's alpha value is 0.973. The HOSI is a scale consisting of a total of 7 sub-scales including activities of daily living (medications, activities of daily living, community and follow-up, feelings about the condition, treatment and complications, quality of life, skin care) and 50 items graded with 5 Likert-type scoring that determine the learning needs of individuals. The scale is evaluated on each subscale and the total scale score. The minimum score is 50 and the maximum score is 250 (Table 1). High scores indicate the level of importance of learning needs. By dividing the total scale and all subscales by the number of questions, the scale and subscale scores are interpreted between 1 and 5 according to the level of importance; "1= not important", "2= somewhat important", "3= neither less nor more important", "4= very important", "5= extremely important".[7]

Data Evaluation

Data were transferred to IBM SPSS Statistics 21 program and frequency distribution was used for categorical variables and descriptive statistics were used for numerical variables. The difference between two groups was analyzed by independent sample t test and the difference between more than two groups was analyzed by one-way analysis of variance (One Way ANOVA). As a result of ANOVA, Levene's test was performed for homogeneity of variance, and then the group or groups from which the difference originated were checked by "multiple comparison test" (Tukey). Tukey test was used to examine the difference between groups in variables that provided variance homogeneity. Pearson correlation analysis was used to examine the relationship between numerical measurements and multiple linear regression analysis was used to examine the factors affecting the scale score, and Cronbach alpha value was used for scale reliability. For significance, $p<0.05$ was accepted.

3. RESULTS

The mean age of the patients was 65.03±6.88 years, 78.3% were female and 21.7% were male. The mean Body Mass Index was 29.58±3.52, the clinical diagnosis was gonarthrosis and the mean duration of hospitalization (days) was 5.30±1.69. Spinal anesthesia was performed in 88.3% of the patients. 68.3% were primary school graduates or higher, 56.7% were single, 80% had income equal to expenses, 46.7% lived with their spouses, 68.3% lived in the district, 46.7% lived on the 1st floor, 16.7% had an elevator in their house,

68.3% had an alafranga toilet inside the house, and 80% had very good financial and moral support from family and environment (Table 2).

While 55% of the patients had chronic diseases, 69.7% of those with chronic diseases had hypertension. 55% of the patients were on continuous medication, 1.7% had allergy (Alfacillin allergy). 81.7% of the patients were non-smokers, while no patient used alcohol. Of those who smoked, 8.3% used 1 pack/day, 48.3% had a history of a different surgery. 98.3% had a permanent companion, 50% were cared for by a child, 61.7% had been hospitalized before. All patients and caregivers had received discharge training for home care (Table 3).

Patient learning needs scale score was 168.90±32.34. The importance level score of the Patient Learning Needs Scale was 3.37. When the importance levels of the subgroups were analyzed, it was found that the highest importance level score belonged to the sub-dimension of treatment and complications (3.65) (very important). This was followed by medications (3.49) (very important), life activities and skin care (3.40), quality of life (3.38), community and follow-up (3.26), and feelings about the condition (2.66) (neither more nor less important), respectively (Table 4).

There was no significant difference between gender and total scale and sub-dimensions of patient learning needs (p=0.563), but there was a statistically significant difference between type of anesthesia and feelings about the condition (p=0.001); between educational status and treatment and complications (p=0.048); between income status and quality of life (p=0.037) skin care (p=0.001) and total scale (p=0.043); and between marital status and patient learning needs scale and sub-dimension scores (p=0.008). Accordingly, those who had spinal anesthesia, those who had primary school or higher education compared to illiterate, those who were single and those whose income was less than their expenses had higher levels of importance of patient learning needs (Table 5).

While there was no statistically significant difference between the place of residence, floor of the house, financial and moral support from family and environment in terms of patient learning needs scale and sub-dimension scores; patient learning needs scale and medications, community and follow-up, emotions related to the situation, quality of life sub-dimension scores between the people living together; There is a statistically significant difference between the presence of an elevator at home in terms of patient learning needs scale and medications, community and follow-up, emotions related to the situation, and skin care sub-dimension scores; and between the presence of a toilet in the place of residence in terms of patient learning needs scale and medications, community and follow-up, emotions related to the situation, and skin care sub-dimension scores (p=0.028). Accordingly, it was found that patients living alone had higher levels of significance in the total patient learning needs scale and in the sub-dimensions of medications, community and follow-up, feelings about the situation, and quality of life. It was found that patients who did not have an elevator at home had higher levels of significance than those who had an elevator in the total patient learning needs scale and its sub-dimensions (Table 6). Patients who had a toilet in the house and who had an alpha-flush toilet had higher levels of significance than those who had an alpha-flush toilet in the patient learning needs scale and its sub-dimensions of medications, community and follow-up, feelings about the situation, and skin care (Table 7).

There is no statistically significant difference between chronic disease, continuous medication use, smoking and alcohol use in terms of patient learning needs scale and sub-dimension scores, while there is a statistically significant difference between previous surgery and feelings related to the situation (p=0.027), treatment complications (p=0.048) and previous hospitalization and skin care (p=0.040) in terms of patient learning needs scale and sub-dimension scores. Accordingly,

while the significance levels of those who have not undergone surgery before are higher than those who have undergone surgery in the sub-dimensions of feelings about the situation and treatment complications sub-dimensions of the patient learning needs scale, the significance levels of those who have not been hospitalized before are higher than those who have been hospitalized before in the skin care sub-dimension of the patient learning needs scale (Table 8).

In the multiple regression analysis examining the factors affecting the patient learning needs scale score, it was found that marital status had a statistically significant effect (p=0.008). Accordingly, the patient learning needs scale score of those whose marital status was single was 21.950 units lower than married patients (Table 9).

Table 1.

Items and scores of the Patient Learning Needs Scale (PLNS) and subscales

Scale and Subscales	Number of Articles	Article Numbers	Minimum and Maximum Values
Medicines	8	3,8,16,18,37,39,44,45	8-40
Life Activities	9	2,5,14,17,27,28,29,30,48	9-45
Community and Monitoring	6	6,9,22,31,36,41	6-30
Feelings about the Situation	5	7,24,32,35,42	5-25
Treatment and Complications	9	1,4,10,19,20,23,26,38,47	9-45
Quality of Life	8	11,13,15,21,34,40,46,50	8-40
Skin Care	5	12,25,33,43,49	5-25
Total	50		50-250

(Çatal and Dicle 2008)

Table 2.

Analysis of findings related to demographic characteristics of patients

		n	%
Age	mean±ss (min-max)	65.03±6.88 (50-77)	
Gender	Woman	47	78.3
	Male	13	21.7
Boy	mean±ss (min-max)	158.83±6.80 (144-179)	
Weight	mean±ss (min-max)	74.63±10.59 (60-112)	
BMI (Body Mass Index)	mean±ss (min-max)	29.58±3.52 (23.80-41.40)	
Clinical diagnosis	Gonarthrosis	60	100.0
Duration of hospitalization (days)	mean±ss (min-max)	5.30±1.69 (2-11)	
Type of anesthesia	Spinal	53	88.3
	General	7	11.7
Education status	Illiterate	19	31.7
	Primary school and above	41	68.3
Marital status	Married	26	43.3
	Single	34	56.7
Employment status	Not working	60	100.0
Income status	Income less than expenditure	10	16.7
	Income equal to expenditure	48	80.0
	Income more than expenditure	2	3.3
People living together	Alone	16	26.7
	Wife	28	46.7
	Spouse and children	7	11.7
	Children	9	15.0
Place of residence	City center	6	10.0
	District	41	68.3
	Village	13	21.7
Floor of the house lived in	Floor	11	18.3
	1st floor	28	46.7
	2nd floor	5	8.3
	3rd floor and above	16	26.7
Presence of an elevator at home	Yes	10	16.7
	No	50	83.3
Availability of toilet facilities in the place of residence	The toilet is inside the house and is saturated	19	31.7
	The toilet is inside the house and it's a laundromat	41	68.3
Material and moral support from family and environment	Very good	48	80.0
	Good.	12	20.0

Table 3.

Examination of health history characteristics of patients

		n	%
Presence of chronic disease	Yes	33	55.0
	No	27	45.0
Chronic diseases	Hypertension	23	69.7
	Diabetes	4	12.1
	Heart disease	4	12.1
	Rheumatic disease	1	3.0
	Other	1	3.0
Continuous medication use	Yes	33	55.0
	No	27	45.0
Presence of allergy	Yes	1	1.7
	No	59	98.3
The presence of allergy to what	Allergy to alfacillin (antibiotic)	1	1.7
	No	59	98.3
Smoking status	Does not use	49	81.7
	Uses	11	18.3
Pack of cigarettes smoked per day	1 package/day	5	8.3
	2 packs/day	5	8.3
	Does not use	49	81.7
	Half a pack/day	1	1.7
Frequency of alcohol consumption	Does not use	60	100.0
Previous surgery status	Yes	29	48.3
	No.	31	51.7
Availability of a companion	Continuously available	59	98.3
	There are certain time intervals	1	1.7
Degree of closeness of the caregiver	No	1	1.7
	My wife	29	48.3
	Children	30	50.0
Previous hospitalization	Yes	37	61.7
	No	23	38.3
Status of receiving discharge training for home care	Yes	60	100.0
Status of the caregiver's discharge training	Yes	60	100.0

Table 4.

Descriptive statistics and distribution of significance level scores of the Patient Learning Needs Scale (PLNS) and its subscales

	Mean	ss	Min	Max	Significance Levels	Cronbach's alpha
PLNS	**168.90**	**32.34**	**80**	**249**	**3.37**	**0.973**
Medicines	27.93	5.09	13	40	3.49	
Life activities	31.08	6.44	17	45	3.40	
Society and monitoring	19.60	4.13	10	30	3.26	
Emotions about the situation	13.33	4.56	5	25	2.66	
Treatment and complications	32.87	5.99	18	45	3.65	
Quality of life	27.05	5.39	12	40	3.38	
Skin care	17.03	3.15	5	25	3.40	

Table 5.

Examination of the Relationship between the Patient Learning Needs Scale and its Subscales and Demographic Characteristics of Patients

	Medicines	Life activities	Society and monitoring	Emotions about the situation	Treatment and complications	Quality of life	Skin care	PLNS
	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss
Gender								
Woman	27.78±5.36	30.68±6.46	19.44±4.37	13.29±4.59	32.55±6.29	26.95±5.78	16.89±3.31	167.62±33.99
Male	28.46±4.07	32.53±6.41	20.15±3.13	13.46±4.59	34.00±4.76	27.38±3.75	17.53±2.53	173.53±26.09
t/p	-0.419/0.676	-0.918/0.362	-0.543/0.588	-0.113/0.909	-0.768/0.445	-0.250/0.802	-0.649/0.518	-0.581/0.563
Type of anesthesia								
Spinal	28.24±5.26	31.50±6.47	19.71±4.26	14.00±4.31	33.13±5.91	27.35±5.51	17.16±3.29	171.13±32.96
General	25.57±2.69	27.85±5.55	18.71±2.92	8.28±3.09	30.85±6.59	24.71±3.81	16.00±1.52	152.00±22.04
t/p	1.313/0.194	1.421/0.160	0.601/0.550	**3.382/0.001***	0.943/0.349	1.225/0.225	0.921/0.360	1.486/0.142
Education status								
Illiterate	26.31±4.06	28.89±5.23	18.68±3.24	12.00±3.77	30.63±5.64	25.57±4.42	16.21±1.61	158.31±25.16
Primary school and above	28.68±5.38	32.09±6.75	20.02±4.44	13.95±4.79	33.90±5.91	27.73±5.70	17.41±3.60	173.80±34.34
t/p	-1.701/0.094	-1.825/0.073	-1.174/0.245	-1.561/0.123	**-2.019/0.048***	-1.453/0.151	-1.785/0.079	-1.756/0.084
Marital status								
Single	29.38±5.65	32.73±6.87	20.70±4.37	14.91±4.67	34.32±6.07	28.64±5.70	17.70±3.78	178.41±35.29
Married	26.03±3.51	28.92±5.19	18.15±3.33	11.26±3.51	30.96±5.40	24.96±4.19	16.15±1.75	156.46±23.21
t/p	**2.809/0.006***	**2.356/0.021***	**2.475/0.016***	**3.318/0.001***	**2.226/0.029***	**2.770/0.007***	**2.110/0.039***	**2.746/0.008***
Income status								
a. Income less than expenditure	27.80±3.67	31.70±5.16	19.40±3.47	12.60±3.30	33.20±4.39	26.20±3.67	17.10±2.37	168.00±23.21
b. Income is equal to expenditure	28.31±4.99	31.39±6.44	19.85±4.12	13.70±4.70	33.18±6.01	27.60±5.32	17.33±2.83	171.39±32.00
c. Income is more than expenditure	19.50±9.19	20.50±4.94	14.50±6.36	8.00±4.24	23.50±7.77	18.00±8.48	9.50±6.36	113.50±47.37
F/p	3.082/0.053	2.987/0.058	1.667/0.197	1.701/0.191	2.675/0.077	**3.467/0.037*(a)**	**7.176/0.001*(a)**	**3.325/0.043*(a)**

a.b.c: indicates mean differences between groups (Tukey)

F: One-way ANOVA test. t: Independent sample t test:p<0.05*

Table 6.

Examination of the Relationship between the Patient Learning Needs Scale and its Subscales and Demographic Characteristics (continued)

	Medicines	Life activities	Society and monitoring	Emotions about the situation	Treatment and complications	Quality of life	Skin care	HÖGÖ
	mean±ss	**mean±ss**	**mean±ss**	**mean±ss**	**mean±ss**	**mean±ss**	**mean±ss**	**mean±ss**
People living together								
a. Alone	25.31±2.52	28.62±4.70	17.12±3.38	11.37±3.15	30.75±4.64	24.81±3.88	15.81±1.64	153.81±19.81
b. Spouse	29.46±4.50	32.96±6.13	21.07±3.32	15.00±4.38	34.75±4.59	28.82±4.06	17.96±2.92	180.03±27.77
c. Spouse and children	29.85±8.97	32.42±9.43	20.57±6.02	14.42±5.59	34.14±9.11	28.71±9.44	17.00±6.19	177.14±53.94
d.Children	26.33±4.71	28.55±6.14	18.66±4.24	10.77±4.49	29.77±7.52	24.22±5.54	16.33±2.00	154.66±31.82
F/p	**3.210/0.029*(a)**	2.272/0.090	**3.886/0.013*(a)**	**3.779/0.015*(a)**	2.711/0.053	**3.330/0.025*(a)**	1.838/0.150	**3.361/0.024*(a)**
Place of residence								
City center	25.33±8.38	28.66±7.84	19.66±5.16	10.33±5.85	31.33±9.41	24.50±7.89	16.00±5.58	155.83±46.76
District	28.17±4.95	31.46±6.45	19.43±4.37	13.73±4.42	32.75±5.93	27.36±5.47	17.31±2.77	170.24±32.34
Village	28.38±3.54	31.00±6.01	20.07±2.92	13.46±4.19	33.92±4.40	27.23±3.65	16.61±3.01	170.69±25.44
F/p	0.874/0.422	0.485/0.617	0.115/0.891	1.485/0.234	0.397/0.673	0.743/0.480	0.594/0.555	0.536/0.587
Floor of the house lived in								
Floor	27.63±4.75	30.90±6.65	20.18±3.91	13.09±4.90	33.36±5.02	27.27±5.06	16.54±3.55	169.00±31.81
1st floor	28.50±5.21	31.96±6.83	19.92±4.31	14.21±4.27	32.96±6.36	27.42±5.56	17.32±2.85	172.30±33.46
2nd floor	28.20±9.28	31.20±9.23	19.80±6.30	14.60±5.89	32.80±9.03	27.40±9.20	16.40±6.65	170.40±54.94
3rd floor and above	27.06±3.67	29.60±4.81	18.56±3.32	11.56±4.25	32.30±5.37	26.10±4.19	17.06±1.91	162.37±23.41
F/p	0.278/0.841	0.437/0.726	0.460/0.711	1.313/0.278	0.060/0.980	0.207/0.890	0.224/0.879	0.313/0.815
Presence of an elevator at home								
Yes	26.40±3.80	30.40±5.60	19.10±2.37	9.90±4.04	32.30±5.96	25.10±3.81	16.80±1.22	160.00±23.09
No.	28.24±5.28	31.22±6.64	19.70±4.40	14.02±4.37	32.98±6.04	27.44±5.59	17.08±3.41	170.68±33.78
t/p	-1.043/0.300	-0.364/0.716	-0.416/0.678	**-2.751/0.007***	-0.325/0.746	-1.259/0.212	-0.451/0.653	-0.952/0.344

a.b.c: indicates mean differences between groups (Tukey)

F: One-way ANOVA test. t: Independent sample t test:p<0.05*

Table 7.

Examination of the Relationship between the Patient Learning Needs Scale and its Subscales and Demographic Characteristics (continued)

	Medicines	Life activities	Society and monitoring	Emotions about the situation	Treatment and complications	Quality of life	Skin care	PLNS
	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss
Availability of toilet facilities in the place of residence								
The toilet is inside the house and is saturated	30.26±5.07	33.21±7.27	21.36±4.17	15.36±4.80	34.78±5.71	29.00±5.28	18.21±3.58	182.21±34.41
The toilet is inside the house and it's a laundromat.	26.85±4.78	30.09±5.85	18.78±3.88	12.39±4.16	31.97±5.96	26.14±5.25	16.48±2.81	162.73±29.76
t/p	**2.519/0.014***	**1.771/0.081**	**2.344/0.022***	**2.452/0.017***	1.721/0.090	1.953/0.055	**2.020/0.047***	**2.243/0.028***
Material and moral support from family and environment								
Very good	27.75±4.97	30.95±6.23	19.52±3.77	13.06±4.31	32.72±5.80	27.00±5.21	16.85±3.09	167.87±31.02
Good.	28.66±5.72	31.58±7.50	19.91±5.50	14.41±5.48	33.41±6.90	27.25±6.26	17.75±3.41	173.00±38.36
t/p	-0.554/0.581	-0.298/0.766	-0.294/0.769	-0.919/0.361	-0.353/0.725	-0.142/0.887	-0.879/0.382	-0.487/0.627

F: One-way ANOVA test. t: Independent sample t test:p<0.05*

Table 8.

Examination of the Relationship between the Patient Learning Needs Scale and its Subscales and Demographic Characteristics (continued)

	Medicines	Life activities	Society and monitoring	Emotions about the situation	Treatment and complications	Quality of life	Skin care	PLNS
	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss
Presence of chronic disease								
Yes	27.48±4.56	30.33±6.44	19.15±3.75	12.66±3.84	32.30±5.79	26.57±4.57	16.69±2.25	165.21±28.72
No.	28.48±5.71	32.00±6.45	20.14±4.54	14.14±5.26	33.55±6.25	27.62±6.28	17.44±3.99	173.40±36.31
t/p	-0.751/0.455	-0.996/0.323	-0.929/0.356	-1.258/0.213	-0.803/0.424	-0.750/0.455	-0.865/0.391	-0.976/0.332
Continuous medication use								
Yes	27.72±4.30	30.75±6.05	19.36±3.65	12.87±3.77	32.81±5.50	26.84±4.43	16.87±2.27	167.27±27.34
No.	28.18±5.99	31.48±6.99	19.88±4.69	13.88±5.38	32.92±6.63	27.29±6.44	17.22±4.01	170.88±38.01
t/p	-0.343/0.732	-0.429/0.668	-0.487/0.627	-0.822/0.414	-0.068/0.945	-0.317/0.751	-0.395/0.694	-0.427/0.670
Smoking and alcohol use								
Does not use	28.20±5.41	31.36±6.63	19.73±4.41	13.65±4.63	33.08±6.40	27.26±5.80	17.16±3.35	170.46±34.47
Uses	26.72±3.16	29.81±5.60	19.00±2.56	11.90±4.06	31.90±3.64	26.09±2.87	16.45±2.06	161.90±19.94
t/p	0.867/0.389	0.717/0.475	0.530/0.597	1.150/0.254	0.583/0.561	0.978/0.335	0.670/0.504	0.790/0.432
Previous surgery status								
Yes	26.72±5.55	29.72±7.19	18.86±4.40	12.00±4.74	31.27±6.82	25.79±5.85	16.24±3.42	160.62±35.45
No.	29.06±4.41	32.35±5.46	20.29±3.78	14.58±4.06	34.35±4.71	28.22±4.70	17.77±2.71	176.64±27.46
t/p	-1.813/0.074	-1.600/0.114	-1.349/0.182	**-2.267/0.027***	**-2.019/0.048***	-1.779/0.080	-1.925/0.059	-1.964/0.054
Previous hospitalization								
Yes	27.02±4.95	30.24±6.49	19.08±3.91	12.48±4.24	31.75±6.13	26.08±5.18	16.37±2.95	163.05±31.25
No.	29.39±5.06	32.43±6.26	20.43±4.40	14.69±4.80	34.65±5.39	28.60±5.45	18.08±3.23	178.30±32.48
t/p	-1.780/0.080	-1.287/0.202	-1.241/0.219	-1.863/0.067	-1.858/0.068	-1.799/0.077	**-2.100/0.040***	-1.810/0.075

t:Independent sample t test:p<0.05*

Table 9.

Multiple regression analysis of the factors affecting the Patient Learning Needs Scale score

	Unstandardized coefficient		Standardized coefficient	t	p	95.0% CI	
	B	Std. Error	Beta			Lower limit	Upper limit
HÖGÖ							
(Fixed)	200.362	12.122		16.529	0.000	176.098	224.626
Marital status	-21.950	7.993	-0.339	-2.746	0.008	-37.949	-5.951

(F:7.542. p:0.008. R2 :0.115)

4. DISCUSSION

When the importance levels of the scale subgroups were analyzed, it was seen that the highest importance level score was treatment and complications, followed by medications, life activities and skin care, quality of life, community and follow-up, and feelings about the situation, respectively. Similarly, in the study of Dursun and Yılmaz (2015), the highest medications and treatment complications sub-dimension was observed.[8] In this context, the fact that patients want to be informed about their treatment, the desire to learn about the complications that may occur in the postoperative process, their medication use after discharge, and the need to learn about issues such as skin care and quality of life. In addition, the variability in the results may be due to the fact that the sample group in the study was different and had different socioeconomic and educational levels.

Length of stay is accepted as a criterion for the quality of care and health assessment. According to this acceptance, shortening the length of hospitalization is important in terms of reducing the cost burden of care and preventing complications such as infection that may occur with an increase in the length of hospitalization.9 In the study of Şahin and Türe, it was concluded that the use of general anesthesia increased the duration of hospitalization in the study affecting the duration of operation, patient and hospitalization after surgery.[10] In this study, the average length of stay (days) of the patients was 5.30±1.69, which was due to the fact that the majority of the patients underwent spinal anesthesia and therefore the length of stay was short.

In the study, 88.3% of the patients underwent spinal anesthesia. There was a significant difference between the emotions sub-dimension of the patients' learning needs scale and the type of anesthesia; the higher importance of patient learning needs of patients with spinal anesthesia may be attributed to their lack of knowledge about spinal anesthesia and their thoughts about how their bodies will adapt after anesthesia and how they will express their feelings about the disease.

Between educational status and treatment and complications, which are sub-dimensions of the scale, it was found that those with an educational status of primary school and above needed more education, especially in the sub-dimension of treatment and complications, than those who were illiterate. Similarly, in the study of Tan et al. (2013), the mean scores of medications and quality of life of those with high school and above education were found to be higher than other education level groups.[11] In the study conducted

by Çetinkaya and Aşiret (2017), it was found that patients' expectations increased and learning needs were higher as the educational level increased[12]; similarly, in the study of Dursun and Yılmaz (2015) on patient learning needs, it was found that the need for education was higher with increasing educational level8. On the other hand, in the study conducted by Gök and Faydalı, no significant relationship was found between the level of education and learning needs, but it was observed that the need for information increased with increasing education level[13]. These results, in line with the literature, show that as the level of education increases, the learning needs of the patients also increase and they have more awareness about the disease and its treatments.

In terms of marital status and patient learning needs scale and sub-dimension scores, it was found that single patients had higher learning needs. Similarly, in the study of Özdelikara et al. (2013), the mean scores of quality of life, medications and community and follow-up sub-dimensions showed that the learning needs of single patients were met more than married patients; according to the study of Doğan et al. (2019), it was observed that the learning needs of single patients were met more than married patients[11,14] On the other hand, Uzun and Demirkıran (2012) found that marital status did not have much effect on learning needs.[15] The higher learning needs of singles in the study may be due to the fact that single individuals have to bear everything alone during the surgery process and adaptation to the situation.

In terms of the patient learning needs scale and sub-dimension scores between the status of having surgery before and the sub-dimensions of emotions related to the situation, the patient learning needs, especially the emotions related to the situation and treatment complications sub-dimension scores of those who have not had surgery before are higher than those who have had surgery before. Similarly, in the study conducted by Yılmaz and Dursun (2015), the average scale sub-dimension and scale total scores were found to be higher in patients who had not undergone surgery before.8 In this context, in line with the literature, it can be concluded that patients without any previous ex perience need more education about the surgical process and postoperative complications that may occur.

Between previous hospitalization status and skin care in the scale sub-dimensions; it was found that patients who had not been hospitalized before had higher learning needs. Similarly, in the study of Yılmaz and Dursun (2015), those who had not been hospitalized before had higher averages of scale sub-dimension and scale total scores.8 This result may be thought to be caused by situations such as being uninformed about the process to be experienced due to the lack of previous hospital experience and fear of the operation process.

In this study, in terms of income status and patient learning needs scale and quality of life and skin care sub-dimensions, learning needs in the total scale and quality of life and skin care sub-dimensions were found to be higher in those whose income was less than their expenses. In the study conducted by Eskicioğlu et al. (2019) in the literature, no significant difference was found between income status and learning needs.[16] In this context, the reason why the learning needs of patients with low income expenses were found to be higher may be explained by the fact that they think too much about the postoperative care burden and the cost dimension brought by the disease.

In this study, although there was no significant relationship between material and moral support from family and environment and patient learning needs scale and sub-dimension scores, human

being is a social being in every aspect and the effect of social and cultural environment on health is inevitable. It can be thought that patients with more material and moral support from the environment will have a faster recovery and adaptation process to the prosthesis.[17] Motivation is one of the important factors that determine the individual's willingness to learn, the psychological support of the environment positively affects the patient's willingness to learn and is considered important for discharge education to be provided with good communication.[18]

5. CONCLUSION

In conclusion, the study conducted to determine the post-discharge learning needs of patients who underwent total knee replacement surgery showed that the learning needs of the patients were moderately important. When the importance levels of the scale subgroups were analyzed, treatment and complications had the highest importance level score, followed by medications, life activities and skin care, quality of life, community and follow-up, and feelings about the situation.

Recommendations for better nursing care and discharge education after a study on the determination of learning needs after total knee replacement surgery and discharge;

Since the group with total knee replacement surgery is generally in the advanced age group, it is very important for nurses to master the body systematics for the advanced age group while providing care and communicating with the patient (in care, determining learning needs, during discharge education, etc.).

When determining the learning needs of the individual, it should not only be centered on the individual, it should be approached systematically by considering the caregivers and providing discharge training. Thus, it is thought that repeated hospitalizations can be prevented, health care costs will be positively affected, and unnecessary emergency hospitalizations can be prevented.

From the moment the patient is hospitalized, he/she should be observed in terms of learning needs on discharge. During the time in the hospital, the patient's information needs should be met in line with the care plans.

In addition, more detailed analysis of the sub-dimensions with higher learning needs will contribute to the literature to understand the specific expectations of patients on these issues. It is also recommended that patients be followed up periodically after discharge to evaluate the new educational needs they encounter at home, and to evaluate variables such as mental health status and social support of patients to examine the effect of psychosocial factors on learning needs. With these recommendations, important contributions can be made to individualize and increase the effectiveness of patient education programs for future studies.

Conflict of interest statement

The authors declared that there was no conflict of interest.

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Ethics approval

Ethics Committee Approval was obtained from SBÜ Yüksek İhtisas Training and Research Hospital University Research Ethics Committee (Ethics Committee Approval Number: 2011-KAEK-25 2022/07-23) before the collection of research data.

Author Contributions

Study design: EC, HCA; Data collection: EC, HCA;

Data analysis: EC, HCA; Study supervision: HCA; Manuscript writing: EC, HCA; Critical revisions for important intellectual content: EC, HCA

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Research Article

A Comparison of Clinical Examination and Magnetic Resonance Imaging Results with Arthroscopy Results in Knee Intra-Articular Pathologies

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Objective: We aimed to determine in which of the symptomatic intra-articular pathologies of the knee, clinical examination and magnetic resonance imaging (MRI) can be an alternative to diagnostic arthroscopy.

Materials and Methods: Prospective analysis of 50 patients aged 18 to 50 years who underwent arthroscopy with the diagnosis of meniscus tear, cruciate ligament injury, cartilage damage, or plica between 2013 and 2015 was conducted. The results of the physical examination and MRI were compared with arthroscopy findings.

Results: Patients with a mean age of 35 years. Sensitivity, specificity, and accuracy rates in the Mc-Murray test were 90%, 11%, 76%; 76%, 33%, 68% in the Apley test; and 80%, 33%, 72% in the Ege's test. Sensitivity, specificity, and accuracy rates in the MRI for the medial meniscus were 87%, 68%, 80%; 92%, 92%, 92% for the lateral meniscus; 36%, 95%, 62% for chondral injury; 90%, 95%, 94% for the anterior cruciate ligament; and 21%, 59%, 34% in the plica.

Conclusion: It should be noted that positive results can also be obtained in other knee intra-articular pathologies other than meniscus tear, as the sensitivity of these tests used to diagnose meniscus tear is high, but specificity is low. 1.5-tesla MRI has a high accuracy rate for detecting meniscus and anterior cruciate ligament injuries, while the diagnostic power of chondral surface evaluation remains limited, and high-resolution cartilage-specific images are required. As it is insufficient for evaluating plica on its own, it must be carefully incorporated during arthroscopy.

Keywords: Chondral lesion, Knee, Magnetic resonance imaging, Meniscus, Plica

1. INTRODUCTION

The knee joint is the largest and most complex joint of the human body. The knee joint is covered by a thin layer of muscle from the front. Due to this structure's inherent weakness, it is susceptible to direct and rotational traumas that cause injury to intra-articular anatomical structures.[1]

Symptomatic intra-articular pathologies are mostly caused by meniscus tears, cruciate ligament tears, cartilage damage, and plica. In the past, these pathologies were evaluated with a medical history, physical examination, and direct X-ray. When necessary, they were examined with arthrography, or direct open surgery was performed. In this algorithm, it was found over time that the patients were exposed to unnecessary surgery or that the surgery was delayed. Physical examination alone was found to be insufficient in detecting intra-articular knee pathologies, particularly meniscus tears.[2] Given that meniscus tears are the most common reason for knee arthroscopy in many clinics, the significance of diagnostic techniques can be better understood.

The prevalence of magnetic resonance imaging (MRI) devices and advances in imaging technology have led to an increase in their utilization. Its

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advantages include being non-invasive, not emitting ionizing radiation, providing multiplanar images, and detecting additional injuries.[3,4] However, the accuracy of MRI in detecting these intra-knee pathologies varies widely among studies ranging from 45 to 98%.[4-6]

Accurate and timely diagnosis is essential for minimizing morbidity caused by intra-articular knee pathologies and optimizing potential performance. In our study, we aimed to investigate the avoidability of diagnostic arthroscopy based on the clinical examination and MRI findings of the patients with meniscus or cruciate ligament injuries who underwent arthroscopic diagnosis and treatment, and the MRI findings of patients with chondral damage or pathological plica.

2. MATERIALS AND METHOS

Ethics committee approval was obtained for this study and decision number 2014/148. Verbal and written confirmation documents were acquired from the patients for participation in the research. Fifty knees of fifty patients aged 18–50 who underwent arthroscopic intervention at a tertiary university hospital from 07.2013 to 07.2015 with a preliminary diagnosis of knee intra-articular pathology were evaluated. McMurray, Apley, and Ege tests were performed as physical examination tests in patients presenting with one or more of the following complaints: knee pain, swelling, locking, or a hollow feeling, and an additional anterior drawer test was performed in patients with suspected cruciate ligament injuries. When significant positive results were obtained in at least one of the tests, axial, sagittal, and coronal sections were acquired in T1 and T2 sequences with a thickness of 2 mm in the supine position in full extension of the knee with a Siemens magnetom aera MRI device with 1.5-tesla power in the radiology department of our hospital. The MRIs were evaluated by a radiologist with expertise in the musculoskeletal system. The arthroscopic results of the patients were considered the gold standard, and the findings of the arthroscopy were compared with those of the physical examination and MRI. Preoperative physical examinations of all patients were performed by us. All MRIs were assessed by the same radiologist. Intraoperative arthroscopy results were determined by an orthopedic specialist with expertise in knee arthroscopy.

McMurray, Apley, and Ege tests were performed in patients presenting with at least one of the complaints of pain, swelling, locking, or feeling of hollowness in the knee.[7-9] When at least one of the tests yielded positive results, T1 and T2 sequences of axial, sagittal, and coronal sections were acquired in supine position and with the knee in full extension using a 1.5-tesla Siemens magnetomaera MRI device. The images were assessed by a radiologist with expertise in the musculoskeletal system. The arthroscopy results of patients who underwent knee arthroscopy surgery after imaging were considered the gold standard. Physical examination tests and MRI findings were compared with arthroscopy results.

Meniscus tears were graded according to signal change on MRI. Grade 3 signal changes were accepted as a tear.[10,11] The outerbridge classification was used to grade cartilage damage.[12] Band appearances with high signal intensity on MRI and low signal intensity in joint fluid were accepted as pathologic plica when seen in the medial, lateral, and infrapatellar regions.[13] The loss of continuity in consecutive sections of the cruciate ligaments in any plane in an MRI was considered a tear.

Arthroscopic surgery was performed by an orthopedic surgeon under spinal anesthesia in the supine position with a tourniquet applied to the

thigh. A Wolf brand arthroscopy device and a 30° angle scope was used.

2.1. Statistical analyses

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy rates of MRI and meniscus diagnostic tests according to the results of arthroscopy were determined using a four-by-four crosstab method in the SPSS 21.0 program. The kappa test was performed to determine the reliability and significance of the tests.

3. RESULTS

Of the 50 patients in the study group, 34 were male (68%) and 16 were female (32%), with a mean age of 35. Of the 50 knees, 31 were left and 19 were right. Thirteen (26%) patients had a history of trauma.

The following intra-articular pathologies were detected during arthroscopy: 41 patients had meniscus tears. Of these, 28 involved the medial meniscus, 10 involved the lateral meniscus, and 3 involved both the medial and lateral meniscus. The anterior cruciate ligament (ACL) was partially ruptured in 7 patients, and 3 patients had a total rupture. No posterior cruciate ligament tear was observed. Chondral damages to varying degrees were detected in the medial femoral condyle in 21 patients, the medial tibial condyle in 10 patients, the lateral femoral condyle in 7 patients, and the lateral tibial condyle in 5 patients. 20 patients had infrapatellar and medial plicae together; 7 patients had only infrapatellar plica; 3 patients had only medial plica; and 3 patients had only lateral plicae.

In the preoperative physical examination of 41 patients with meniscus tears, the Mc-Murray test was positive in 37, the Ege's test was positive in 33, and the Apley test was positive in 31. Of the 9 patients who did not have meniscus tears but had at least one of the other intra-knee pathologies, 8 had positive Mc-Murray tests, 6 had positive Ege's tests, and 6 had positive Apley tests.

In our study, the high sensitivity and low specificity rates of diagnostic tests for meniscus compared to arthroscopy results, which we consider the gold standard, were remarkable (table 1).

Three of the ten patients with varying degrees of anterior cruciate ligament injury had a total rupture, while seven had a partial rupture. During the preoperative physical examination of these patients, only those with a total rupture could be diagnosed.

Table 1.

Results of diagnostic tests for meniscus based on arthroscopy results

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
McMurray	90	11	80	20	76
Apley	76	33	84	23	68
Ege	80	33	85	27	72

PPV: Positive predictive value, NPV: Negative predictive value

When we compared the MRI results of intra-articular pathologies of the knee with arthroscopy results, the accuracy ranged from high to low for the anterior cruciate ligament, lateral meniscus, medial meniscus, chondral damage, and plica (Table 2). In addition, kappa values were 57 for the medial meniscus, 80 for the lateral meniscus, 82 for the ACL, and 29 for the chondral surface.

Table 2.

MRI results based on arthroscopy findings

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Medial meniscus	87	68	87	76	80
Lateral meniscus	92	92	80	97	92
Chondral damage	36	95	91	54	62
Anterior cruciate ligament	90	95	82	97	94
Plica	21	59	50	28	34

PPV: Positive predictive value, NPV: Negative predictive value

4. DISCUSSION

Although the accuracy and sensitivity of McMurray, Apley, and Ege's tests, which are frequently used in the physical examination of meniscus injuries, are high, their specificity is low because they can produce highly positive results not only for meniscus pathologies but also for intra-knee pathologies. Total ruptures of the anterior cruciate ligament can be diagnosed through a physical examination, whereas partial injuries cannot be diagnosed solely through a physical examination. 1.5-tesla MRI has a high accuracy rate in the diagnosis of lateral meniscus and cruciate ligament pathologies. Although the accuracy rate for injuries to the medial meniscus is relatively low, it is adequate. In evaluating the chondral surface, diagnostic power is still limited. It is insufficient for detecting the presence of plica.

The use of MRI has increased significantly because it does not emit ionizing radiation, is noninvasive, and is less expensive than arthroscopy for diagnostic purposes.[14] With the widespread use of MRI, clinical questions that required answers began to attract the interest of researchers. The first of these questions is, if a meniscus tear is suspected based on a patient's medical history and physical examination, should an MRI be performed? The second question is: How much should we rely on MRI if there is no pathology after MRI, but the patient has clinical symptoms? The third question is how accurate is arthroscopic intervention based on anamnesis and physical examination findings without MRI? Although there are numerous studies attempting to answer these questions, there are significant differences in the results.[15-18] Weinstabl et al. randomly divided 823 patients with meniscus tears into two groups following physical examination tests. The first group of patients underwent MRI before arthroscopy. Only 2% of these patients had arthroscopies that revealed no positive results. However, when arthroscopy was

performed on the second group of patients with a prediagnosis of meniscus injury based solely on physical examination tests without MRI, meniscus damage could be detected in only 30% of cases.[18]

Similarly, our study demonstrates that physical examination tests are insufficient to diagnose meniscus injuries. Since the McMurray, Apley, and Ege's tests, which we evaluated among the meniscus diagnostic tests in our study, can yield highly positive results in the presence of other intra-knee pathologies without meniscus tears, we recommend that the preliminary diagnosis be supported by MRI with higher accuracy, sensitivity, and specificity rates prior to deciding on arthroscopy. Although all three diagnostic tests for the meniscus were positive in three of the nine patients who did not have meniscus tears during arthroscopy, two of these patients had only plica damage and one had chondral damage.

In a study examining 82 asymptomatic knees, it was reported that the incidence of positive MRI results in terms of meniscus was high even in asymptomatic patients, especially in patients over the age of 50.[19] This is supported by the MRI specificity rate of 68% for the medial meniscus in our study. However, since our study did not include patients over 50 years of age, MRI yielded more reliable results than in this study. For these reasons, we recommend that a preliminary diagnosis be made with physical examination tests before making a surgical decision for meniscus, especially in patients over 50 years of age, and then this preliminary diagnosis should be supported by MRI.

On physical examination, no additional tears were suspected in seven patients with partial ACL tears. Three patients with total ruptures of the ACL were diagnosed on physical examination. Although physical examination is a reliable diagnostic method for total ACL tears, it is usually insufficient for partial tears. Therefore, we recommend MRI in patients who describe an anterior cruciate ligament injury in their history, even if no injury is suspected on physical exam.

The number of intact osteochondral surfaces on arthroscopy was 22, 21 of which were also found to be intact on MRI. In other words, the specificity was quite high (95%). Of the 18 patients with stage 1 and 2 lesions, 13 (72%) were detected on MRI, whereas only 5 (50%) of the 10 patients with stage 3 and 4 lesions were detected on MRI. While a higher ratio of advanced lesions was expected, a higher ratio of low-stage lesions was diagnosed. This conclusion may have been influenced by the small number of patients in whom we evaluated chondral damage and the effects of concomitant pathologies on signal changes. Many studies have reported that cartilage lesions are frequently localized medially.[18-21] In our study, 20 of 28 patients with chondral damage had only medial side involvement.

The literature indicates that the sensitivity of MRI for detecting partial and full-thickness cartilage lesions is between 8% and 100%, while the specificity is between 80% and 100%.[20-24] Our study had a sensitivity of 36% and a specificity of 95%, which is comparable to other studies. Due to the fact that the accuracy rate remained at 62% and higher accuracy rates were observed in cartilage-specific images with high tesla devices in the literature,[25-29] we recommend cartilage-specific images with higher tesla MRI devices for patients with cartilage damage. In the literature, higher-resolution and more specific imaging protocols are recommended for evaluating chondral lesions with MRI. Rather than standard MRI, 3-tesla and 7-tesla MRI with higher magnetic field strength can provide clearer visualization, especially of small chondral lesions and subchondral changes.[30]

Additionally, imaging techniques such as T2 Mapping and T1 Rho, which are used to assess cartilage water content and collagen matrix structure, may enable the detection of early-stage chondral degeneration.[31,32] However, it should be noted that many factors, such as the movement of the patient at the time of shooting, the position of the knee, the experience of the technician performing the shooting, and the presence of additional pathologies, may affect the result. In a study by Yoon et al., the rate of correct diagnosis was 70% in the presence of one pathology, whereas the accuracy rate decreased to 28% in the presence of three or more pathologies.[33] The higher diagnosis rate of stage 2 lesions compared to stage 3 lesions in this study may be attributable to the aforementioned factors.

Physical examination, ultrasonography, and MRI have previously been used as diagnostic tools in the diagnosis of intra-knee plica.[13,34] However, arthroscopy remains the gold standard diagnostic method for identifying plica.[35] In our study, plicas were detected during arthroscopy in 33 of 50 patients. Only 21% of these plicas were detected on MRI. On MRI, plica was considered in 7 of 17 (41%) patients who did not exhibit plica on arthroscopy. The sensitivity, specificity, and accuracy of MRI in diagnosing plica were 21%, 59%, and 34%, respectively; MRI alone cannot be considered a reliable diagnostic tool. Therefore, we recommend that the presence of plica be carefully examined during all arthroscopic procedures.

The limitations of the study include the small number of patients, especially those with ligament injuries, and the lack of cartilage-specific imaging for patients with chondral injuries.

5. CONCLUSION

Meniscus tears and anterior cruciate ligament ruptures can be diagnosed through clinical examination. However, since the specificity of these tests is limited, it should be kept in mind that positive results may be obtained in the presence of other intra-articular pathologies. Therefore, when these tests yield positive results before planning knee arthroscopy, we recommend utilizing MRI to determine the actual source of the pathology and other intra-knee pathologies that may be associated. However, if a clinical examination yields a negative result, a single test should not be used, and the result should be confirmed by multiple tests. Considering the false positive and false negative rates of MRI, arthroscopic intervention should not be recommended with positive MRI results alone without clinical evidence. In cases where complaints persist due to plica and chondral injuries, we do not recommend further postponement of arthroscopic intervention based on negative MRI findings.

Authors Contributions:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rıfat Şahin and Mehmet Sabri Balık. The first draft of the manuscript was written by Rıfat Şahin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing Interest:

The authors declare that they have no conflict of interest. On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Considerations:

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Research Article

Determination of the Traditional and Complementary Medicine Methods Used by Parents for Their 7-14-Year-Old Children with Upper Respiratory Tract Infection and Their Attitudes

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Background: Traditional and complementary medicine methods are used by parents in children with upper respiratory tract infections, and parents should be informed about the side effects that may occur due to these methods. This study was conducted to determine the traditional and complementary medicine methods utilized by parents for their 7-14-year-old children with upper respiratory tract infections and their attitudes.

Method: A descriptive research design was used. The study was conducted between November 2023 and January 2024. Data were collected using a "Socio-Demographic Data Form" and the "Attitude towards Holistic Complementary and Alternative Medicine Scale." A total of 310 parents participated in the study online.

Results: The rate of parents' use of traditional and complementary medicine in children with upper respiratory tract infections was 91.6%. These methods that parents most frequently used were showering the child or tepid sponging in case of fever, giving the child milk with honey, ginger, molasses in case of sore throat, washing the child's nose with salt water in case of nasal congestion, putting a hot towel on the child's ear in case of earache, and giving the child honey-molasses to reduce/cut the cough. Parents' mean score on the Attitude towards Holistic Complementary and Alternative Medicine Scale was found to be 29.51±3.79. As the age of the child (β=1.258) and the economic status of the family (β=2.916) increased, parents' use of traditional and complementary medicine increased, as well.

Conclusion: The majority of parents used traditional and complementary medicine methods for their 7-14-year-old children who had upper respiratory tract infections. It was determined that parents' attitudes towards traditional and complementary medicine methods were positive and moderate.

Keywords: Child, Parents, Respiratory tract infection, Traditional medicine, Complementary medicine, Attitude

1. INTRODUCTION

Traditional and complementary medicine (TCM) practices in children are gradually becoming more common globally.[1] According to the World Health Organization, traditional medicine consists of applications that are used to prevent physical and mental diseases and diagnose and treat them, change according to cultures, and are based on the beliefs and experiences of societies. Complementary medicine is defined as various health practices that are not part of a country's tradition or conventional medicine and are not fully integrated into the health system.[2]

TCM, which is used to treat diseases in children and comfort them, is frequently used in children with upper respiratory tract infections (URTI).[3,4] URTI is among the most common childhood diseases and the most important causes of mortality and morbidity due to infectious diseases.[5,6] It has been determined that the rate of admission to hospital with URTI in children under the age of

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15 has globally increased, with the course of the disease being more severe. In addition, it has been determined that it has caused absenteeism in more than 20 million students.[6,7] According to the 2022 data from the Turkish Statistical Institute, URTI is the most common disease in children in the 0-14 age group. It ranks first in the 7-14 age group with the rate being 27.1%.[8]

Generally, parents turn to TCM methods as they think they are natural and harmless, easy to use, or cheap, do not require invasive interventions, support medical treatments, strengthen the immune system, or reduce disease symptoms. In addition, they use them when they cannot get results from modern medical practices, when they have negative experiences with healthcare personnel in the hospital, because they are afraid of the side effects of medical treatments, or because they find treatment methods painful. Apart from these, low or high socio-cultural level also affects the use of TCM methods.[1,9-13]

Although TCM methods are widely used, it has been determined that parents have inadequate knowledge about the side effects that these methods may have.[1,3] It has been determined that unconscious use of TCM methods affects the outcome of medical treatment and causes side effects.[11,14] To provide better quality and qualified care, doctors/nurses/healthcare workers need to know traditional and complementary medicine methods, their risks, and benefits, identify children using these methods, and inform society and parents.[1,15,16]

This study was carried out to determine the traditional and complementary medicine methods applied by parents for 7-14-year-old children with upper respiratory tract infections and their attitudes.

2. METHOD

2.1. Type and sample of the study

This is a descriptive type of research. The study was conducted with parents who had children aged 7-14 years and lived in the İzmir, Konya, and Hakkari provinces of Türkiye between November 2023 and January 2024. The necessary sample size for the study was calculated as the parents of 195 children on the G*Power 3.0 statistical analysis software, based on the status of children for developing a respiratory system infection, a Type I error of 0.05, a Type II error of 0.20 (a power value of 80%), and a medium effect size. In case the parametric test assumptions were not met, the sample was increased by 10% and the study was planned to be completed with 210 parents. The convenience sample method was used to select samples from the research population. In the study, data were collected using an online questionnaire created on Google Forms from parents through their social media accounts and e-mails. Inclusion criteria for parents were volunteering to participate in the research, literacy in Turkish, and having children between the ages of 7-14. A total of 310 parents participated in the study.

2.2. Data collection

Study data were collected using a "Socio-Demographic Data Form" and the "Attitude towards Holistic Complementary and Alternative Medicine Scale."

2.2.1. Socio-demographic data form

This form was prepared by the researchers following a literature review. It consists of nine questions about parents' age, education level, economic status, number of children, the child's chronic disease, family type, parents' sources of information about the TCM method. It consists of six questions TCM applications in respiratory tract infections (status of applying TCM, application time of TCM, reasons for using TCM methods, status of

benefiting from TCM methods, considering using TCM methods again, status of recommending TCM methods to others). It consists of five questions TCM methods implemented for symptoms of respiratory tract infections (applications for fever, sore throat, nasal congestion, earache, and cough).[15,16]

2.2.2. The Attitude toward Holistic Complementary and Alternative Medicine Scale (AHCAM)

This scale was developed by Hyland et al. in 2003[17], and its validity and reliability in Turkey were tested by Erci in 2003. The scale has two subscales: complementary alternative medicine (CAM) (items 2, 4, 6, 8, 9, and 11) and holistic health (HH) (items 1, 3, 5, 7, and 10). It is a six-point Likert-type scale and consists of 11 questions (1=strongly agree, 6=strongly disagree). Scores on the scale range from 11 to 66. As scores from the scale decrease, positive attitudes toward holistic complementary and alternative medicine increase. Cronbach's alpha value of the scale is 0.72.[18]

2.3. Data analysis

Study data were analyzed on the SPSS 24.0 (IBM SPSS version 24, USA) software. Mean, standard deviation, frequency, and percentage values were used to evaluate descriptive characteristics. The distribution of the data was examined with the skewness-kurtosis normality test. The predictive power of the independent variables on parents' mean scores on the total and subscales of the AHCAM scale was evaluated using a logistic regression analysis. VIF and tolerance analysis were used to determine whether there was multicollinearity between the variables and whether the variables should be included in the regression model. Variables with a VIF value of <10 and a tolerance value of 0.2 were included in the regression model. The significance level was taken as $p<0.05$.

3. RESULTS

The mean age was found as 37.90±5.62 (min=25, max=55) for mothers, 40.15±5.96 (min=28, max=59) for fathers, and 9.88±2.95 (min=7, max=14) for children. The mean number of children was 1.64±0.66 (min=1 and max=4). It was determined that 52.3% (n=162) of the children were female and 47.7% (n=148) were male. According to the results, 69.7% (n=216) of the mothers had completed the questionnaire, and 61.9% (n=192) of the mothers and 63.2% (n=196) of the fathers had an undergraduate degree. It was found that 65.5% (n=203) of the parents had equal income and expenses, 88.1% (n=273) of the children did not have any chronic disease, and 94.2% (n=292) had a nuclear family type. The examination of parents' sources of information about the TCM methods showed that 39.7% (n=123) had learned them from doctors/nurses/healthcare workers and 34.8% (n=108) from family members/relatives (Table 1).

According to parents' statements, 91.6% (n=284) used TCM applications for their children with upper respiratory tract infections. Of the parents who used TCM methods for their children, 49.0% used them before drug treatment, 56.1% used them because they strengthened immunity, 95.8% benefited from the TCM method, 96.8% thought of using them again, and 89.0% recommended the methods to others (Table 2).

The examination of the parents' traditional and complementary medicine methods to reduce fever indicated that 62.9% of the parents showered the child/gave a tepid sponge bath. To relieve a sore throat, 39.9% of the parents gave their children milk with honey. To relieve nasal congestion, 40.0% of the parents washed the child's nose with salt water. To relieve earache, it was found that 38.4% of the parents put a hot towel on the child's ear. To reduce/cut a cough,

32.6% of the parents gave their children honey-molasses (Table 2).

Parents' mean scores on the AHCAM were 21.04±2.96 on the complementary and alternative medicine sub-dimension, 8.47±2.80 on the holistic health sub-dimension, and 29.51±3.79 on the total scale (Table 3).

Logistic regression analysis was used to determine which variables predicted the use of traditional and complementary medicine. The result of the Hosmer and Lemeshow test showed that the model was appropriate and significant. Twelve variables in the model explained 34% of parents' use of traditional and complementary medicine. When the variables were examined one by one, it was determined that the significant variables affecting the parents' use of traditional and complementary medicine were the child's age, the income level of the family, and the scores of complementary alternative medicine and holistic health sub-dimensions. It was determined that the age of the child (β=1.258) increased parents' use of traditional and complementary medicine by 1.258 times, that is, as the age of the child increased, parents' use of traditional and complementary medicine increased. It was determined that the economic status of the family (β=2.916) increased parents' use of traditional and complementary medicine by 2.916 times, that is, as the economic status of the family increased, parents' use of traditional and complementary medicine increased, as well. It was found that the complementary alternative medicine sub-dimension of the AHCAM scale increased parents'use of traditional and complementary medicine by 0.629 times (β=0.629), that is, the use of traditional and complementary medicine by parents who had positive attitudes toward the use of complementary alternative medicine increased. The mean score of the holistic health sub-dimension increased parents' use of traditional and complementary medicine by 0.788 times (β=0.788), that is, the use of traditional and complementary medicine by parents who had positive attitudes toward holistic health increased (Table 4).

Table 1.

Participants' Descriptive Characteristics

Descriptive characteristics	**M±SD**	**Min-Max**
Child's age	9.88±2.95	7-14
Mother's age	37.90±5.62	25-55
Father's age	40.15±5.96	28-59
Number of children	1.64±0.66	1-4
	n	%
The questionnaire respondent		
Mother	216	69.7
Father	88	28.4
Other (caregiver, family member)	6	1.9
Gender		
Female	162	52.3
Male	148	47.7

Mother's education level		
Non-literate	1	0.3
Elementary school	2	0.6
Middle school	11	3.5
High school	74	23.9
Undergraduate	192	61.9
Master's degree/PhD	30	9.7
Father's education level		
Elementary school	4	1.3
Middle school	1	0.3
High school	52	16.8
Undergraduate	196	63.2
Master's degree/PhD	57	18.4
Level of income		
Income=expenses	203	65.5
Income>expenses	86	27.7
Income<expenses	21	6.8
Presence of chronic disease in the child		
Yes	37	11.9
No	273	88.1
Family type		
Core	292	94.2
Extended	18	5.8
Parents' information sources about TCM methods		
Doctor/nurse/healthcare worker	123	39.7
Family members/relatives	108	34.8
Neighbor/friend	28	9.0
TV-Radio	1	0.3
Internet	41	13.2
Book/newspaper/magazine	9	2.9

Table 2.

Parents' Attitudes, Behaviors, and Methods Regarding the Use of Traditional and Complementary Medicine for Children with Upper Respiratory Tract Infections

Traditional and complementary medicine attitudes and behaviors	n	%
Status of applying TCM methods		
Yes	284	91.6
No	26	8.4

Time of applying TCM		
Before medication treatment	152	49.0
With medications	93	30.0
When there is no response to medications	65	21.0
Reasons to use TCM methods		
No benefit of medical treatment	11	3.5
Fearing that medications may have side effects	44	14.2
Having to wait longer times in hospitals	4	1.3
The method is cheap and easily accessible.	13	4.2
It is harmless.	64	20.6
It strengthens immunity.	174	56.1
Status of benefitting from TCM methods		
Yes	297	95.8
No	13	4.2
Considering using TCM methods again		
Yes	300	96.8
No	10	3.2
Status of recommending TCM methods to others		
Yes	276	89.0
No	7	2.3
No knowledge of the methods	27	8.7
Traditional and complementary medicine methods	n	%
Applications to reduce fever		
Shower/tepid sponge bath	195	62.9
Wiping the body with vinegar water	89	28.7
Applying ice to the body	1	0.3
Applying a mixture of aspirin and lemon to the body	25	8.1
Applications to relieve a sore throat		
Using herbal tea (mint-lemon, linden, etc.)	105	33.9
Giving milk with honey, honey with ginger, molasses	121	39.9
Rinsing the mouth with apple vinegar	84	27.1
Applications to relieve nasal congestion		
Washing with salt water	124	40.0
Using vapor	81	26.1
Applying Vicks, thyme oil, or peppermint oil to the sides of the nose	96	31.0
Dropping olive oil into the nose	9	2.9

Applications to relieve earache		
Dropping glycerin/clean water into the ear	43	13.9
Dropping breast milk	50	16.1
Dropping onion juice	63	20.3
Dropping salt water	16	5.2
Dropping olive oil, ozone oil	19	6.1
Putting a hot towel on the ear	119	38.4
Applications to reduce/cut a cough		
Using herbal tea/herbal mixtures	99	31.9
Using honey and molasses	101	32.6
Applying vicks to the body	68	21.9
Massage or keeping warm (placing a towel on the back, etc.)	42	13.5

Table 3.

Mean Scores on the Attitude towards Holistic Complementary and Alternative Medicine Scale (AHCAM) and Its Sub-Dimensions

Scores	Minimum	Maximum	Mean±SD
Complementary and alternative medicine	9.0	30.00	21.04±2.96
Holistic health sub-dimension	5.0	29.00	8.47±2.80
Total AHCAM scale	16.00	45.00	29.51±3.79

Table 4.

Factors that Predicted Parents' Use of Traditional and Complementary Medicine in Children with Upper Respiratory Tract Infections

Variables							%95CI	
	Beta	Standard Error	Wald	Df	Sig.	Exp (B)	Lower	Upper
Child's age	0.230	0.101	5.198	1	0.023	1.258	1.033	1.533
Child's gender	0.074	0.515	0.021	1	0.885	1.077	0.393	2.953
Number of children	-0.210	0.389	0.292	1	0.589	0.810	0.378	1.736
Mother's age	-0.039	0.108	0.130	1	0.719	0.962	0.779	1.188
Mother's education level	0.293	0.390	0.564	1	0.453	1.340	0.624	2.877
Father's age	-0.093	0.106	0.773	1	0.379	0.911	0.741	1.121

Father's education level	-0.088	0.434	0.041	1	0.840	0.916	0.391	2.145
Income level of the family	1.070	0.505	4.488	1	0.034	2.916	1.083	7.849
Chronic illness status of the child	0.443	0.820	0.292	1	0.589	1.557	0.312	7.766
Family type	0.771	1.112	0.481	1	0.488	2.163	0.245	19.125
Complementary alternative medicine sub-dimension	-0.463	0.107	18.878	1	<.001	0.629	0.510	0.775
Holistic health sub-dimension	-0.238	0.067	12.795	1	<.001	0.788	0.692	0.898

Nagelkerke R Square: 0.337; Hosmer and Lemeshow test: Chi-square: 7.185, df: 8, Sig: 0.517; Omnibus test: Chi-square: 49.39, p<0.001.

4. DISCUSSION

Parents' use of TCM in children with upper respiratory tract infections is globally increasing.[1,3,19]Some studies have shown that parents' use of TCM in children with upper respiratory tract infections is high (11.6%-86.0%)[20-22], they use TCM methods before drug treatment, and that they benefit from them.[16,20] The findings of these studies are similar to our research results. The reasons why parents usually turn to TCM methods may have been that hospitals are usually crowded and far away, there is no referral system in family health centers despite easy access to them, parents think that hospitals cannot adequately meet their expectations and demands, some TCM methods can be easily applied in the home environment, and that these methods are considered natural and harmless.[23-25]

The examination of parents' sources of information about TCM methods in the literature indicated that they mostly obtained information from family members and relatives.[16,21, 20,26,27] These studies are not consistent with our research. In this study, doctors/nurses/healthcare workers were the first people to get information about TCM, which was followed by family members/relatives. There was no study in the literature showing that parents received information from doctors/nurses/healthcare workers about TCM methods to use in children with upper respiratory tract infections. It is thought that the reason for this situation may have been that the majority of the parents in our study were university graduates, that is, their education level was high. As a result of this study, we recommend that healthcare personnel, especially pediatric nurses who provide care for pediatric patients, should be informed about TCM methods and their side effects and that parents should also be informed accordingly.[26,28]

When parents' practices of traditional and complementary medicine methods to reduce fever were examined, it was found that most of them showered the child or gave a tepid sponge bath.[15,16,20,27] These studies are similar to our study. It is known that showering the child with warm water and applying a warm compress to decrease fever are correct practices while showering with cold water, applying cold compresses, ice, or a

mixture of aspirin and lemon to the body, and wiping the body with vinegar water are wrong practices.[16,20,29]It was determined that the majority of parents in this study resorted to the correct practice in decreasing fever, that is, they showered the child /gave a tepid sponge bath and that very few of them wiped the body with vinegar water. When the practices of parents to relieve a sore throat were examined, it was found that they gave the child milk with honey, honey with ginger, molasses, and herbal tea (mint-lemon, linden, etc.) and had them rinse their mouth with apple cider vinegar.[15,20] These results are consistent with our research results. Although usage rates vary across studies, the methods used to relieve a sore throat are similar. The practices used by parents to relieve nasal congestion mainly included washing the child's nose with salt water, which was followed by applying Vicks, thyme oil, or peppermint oil to the nose wings, using vapor, and dropping olive oil into the nose.[15,26,20] These results are similar to those of our research. Parents primarily preferred nasal irrigation with saline, especially in cases of nasal congestion, in this study, which was found significant. In the literature, it has been recommended that parents perform nasal irrigation with salt water as an alternative treatment method in cases of nasal congestion in children, especially in chronic and allergic sinusitis.[30,31] When the practices used to relieve earache were examined, it was determined that parents put a hot towel on the child's ear and applied drops of onion juice, breast milk, salt water, olive oil-ozone oil, and glycerin/clean water into the child's ear.[15,20] These studies are similar to our research. Since the effectiveness of these applications has not been fully proven, their use is controversial. The examination of practices to reduce/cut a cough indicated that the first method preferred by parents was to give honey and molasses to the child, and practices such as giving the child herbal tea/herbal mixtures, applying Vicks to the body and massage, or keeping warm (placing a towel on the back, etc.) were also performed.[15,16,27] These results are consistent with our research. Since studies on this subject are limited, more studies are needed.

The evaluation of the findings of this study showed that parents used traditional and complementary medicine practices to reduce fever, relieve a sore throat, nasal congestion, and earache, and reduce/cut a cough, which were not life-threatening practices.

In our study, the mean AHCAM score of the parents was found as 29.51±3.79. In a study conducted in the literature, parents' mean AHCAM score was found to be 26.19±7.52.[26]The results of our study are similar to those in the literature, and it was determined that parents' attitudes toward TCM methods were positive and moderate.

Many factors affect parents' use of traditional and complementary medicine in children.[26,32] In this study, it was determined that the child's age was effective in parents' use of TCM methods. It was found that as the child's age increased, parents' use of TCM increased, as well. It has also been stated in the literature that parents tend to use TCM as the child's age increases.[16]The result of our research is consistent with the literature. On the other hand, there are studies showing that the child's age and using TCM methods are not related.[21]Such a result in this study may have been that parents' use of TCM to cope with this situation may have increased due to the frequent occurrence of respiratory tract infections in crowded and closed environments when children started school. In this study, it was determined that the economic status of the family was effective in parents' use of TCM. It was found that as the economic status of the family increased, parents' use of TCM increased, as well. In a study,

families with high economic status reported that they frequently used TCM for their children.[32] There are studies in the literature showing that income level and TCM use are not related.[26,33,34] This study showed that parents' good economic status allowed them to access TCM methods more easily. Similar to the studies in the literature, no relationship was found in our study between parents' use of TCM and the child's gender, the number of children, parents' age and education level, the child's chronic disease status, and family type.[26,32] The differences or similarities between factors affecting parents' use of traditional and complementary medicine in children with upper respiratory tract infections in our study and other studies may have been due to cultural differences or different measurement tools used to measure traditional and complementary medicine practices.

Limitations of our study:

This study has several limitations. The use of a convenience sample method is a limitation. Therefore, its generalizability may be limited. Another limitation is that parents filled out the questionnaire based on self-report, which may have led to biases. However, it is thought that the participation of parents from three regions of Turkey in the study and the large sample size may have reduced this limitation.

5. CONCLUSIONS

It was determined that parents' attitudes towards TCM methods that they applied to their 7-14-year-old children with upper respiratory tract infections were positive and moderate. The majority of parents used TCM methods for children with upper respiratory tract infections. According to the results, parents applied traditional and complementary medicine methods to their children to intervene in some health disturbances. For example, they preferred showering the child or tepid sponging to reduce fever, giving the child milk with honey, a mixture of ginger and honey, or molasses to relieve a sore throat, washing the child's nose with salt water to relieve nasal congestion, putting a hot towel on the child's ear to relieve earache, and giving the child honey and molasses to reduce/cut a cough. As a result of the logistic regression analysis in the study, it was determined that the age of the child and the economic status of the family were variables that significantly predicted parents' use of traditional and complementary medicine methods. It is recommended to conduct correlational type studies with larger samples to reveal the relationship between sociodemographic characteristics and TCM use. Parents' interest in TCM methods requires all healthcare personnel, especially pediatric nurses, to have comprehensive knowledge about these methods. Parents and society should be educated about the correct use of them.

Declaration of interests:

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions:

Idea/Concept: DDK, ŞD, MB; Design: DDK, ŞD, MB; Control/Supervision: DDK, ŞD, MB; Data Collection and/or Processing: DDK, ŞD; Analysis and/or Interpretation: DDK, MB; Literature Review: DDK, ŞD, MB ektaş; Writing the Article: DDK, ŞD, MB; Critical Review: DDK, ŞD, MB.

Ethics Committee:

The approval of the ethics committee of a university (date: 30.10.2023, decision number: 2023/116-1) and the permission of the author of the scale to be used in the study were obtained. Parents who agreed to participate in the research were asked to read and mark the informed consent section on the online data collection form. Those who checked the approval box were allowed to access

the rest of the data collection form. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Research Article

Impact of Right Ventricular Function on Mortality and Reoperation Rates in Cardiovascular Surgery

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Objective: This study aimed to investigate the impact of preoperative right ventricular (RV) function on postoperative outcomes such as mortality, reoperation rates, valve size, and other clinical variables in patients undergoing tricuspid valve surgery.

Methods: This retrospective study included 100 patients who underwent tricuspid valve surgery. Patients were categorized into four groups based on preoperative RV function: normal, mildly depressed, moderately depressed, and severely depressed. RV function was assessed using echocardiographic parameters, including tricuspid annular plane systolic excursion (TAPSE), tissue Doppler imaging (TDI), mean pulmonary artery pressure (MPAB), and valve size. Postoperative outcomes, including mortality and reoperation rates, were analyzed.

Results: Patients with severely depressed RV function had significantly higher mortality rates (p=0.035). Reoperation rates also increased as RV function worsened (p=0.006). No significant difference was found between groups regarding valve size (p>0.05) or the type of surgery (sternotomy or thoracotomy) (p=0.714).

Conclusion: Right ventricular dysfunction significantly increases postoperative mortality and reoperation rates in patients undergoing tricuspid valve surgery. Careful preoperative evaluation of RV function, including valve size, is critical for improving surgical outcomes.

Keywords: Right ventricular dysfunction, Tricuspid valve surgery, Mortality, Reoperation

1. INTRODUCTION

Right ventricular (RV) function is a critical determinant in the prognosis of patients undergoing cardiovascular surgery, particularly in those involving tricuspid valve surgery.[1,2] The right ventricle, which pumps blood to the lungs, plays a fundamental role in maintaining pulmonary circulation, and its dysfunction can have profound implications on overall cardiovascular outcomes. Cardiovascular surgeries, especially those requiring tricuspid valve interventions, impose unique challenges on the RV.[3] This is primarily due to the anatomical and physiological burden placed on the right heart during and after surgery.[4]

Tricuspid valve surgery, commonly performed to address tricuspid regurgitation or stenosis, increases the RV's workload by altering hemodynamics and increasing the afterload.[5,6] The surgery often involves the placement of a prosthetic valve, either bioprosthetic or mechanical, which, while restoring valve competence, can exacerbate existing RV dysfunction. This is particularly concerning in patients with pre-existing RV impairment, where postoperative RV failure becomes a significant risk factor for adverse outcomes such as increased mortality, prolonged intensive care unit (ICU) stays, and higher reoperation rates.[7,8]

Preoperative RV dysfunction has been identified as a major prognostic factor in several studies.[3,9]

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It is known to correlate with higher morbidity and mortality rates, especially in patients undergoing valve surgeries that involve the right heart. In the context of tricuspid valve surgery, RV dysfunction can compromise surgical outcomes by impairing the heart's ability to adapt to the increased hemodynamic stress post-surgery.[10] This dysfunction may manifest as reduced right ventricular ejection fraction, increased right atrial pressures, and decreased right ventricular longitudinal strain, all of which are associated with poor clinical outcomes.[11,12]

Despite the growing awareness of RV dysfunction's role in surgical outcomes, there remains limited consensus regarding its exact prognostic value, particularly in tricuspid valve surgery. Previous research has predominantly focused on left ventricular dysfunction, often overshadowing the importance of RV function.[13,14] However, with advances in echocardiography and tissue Doppler imaging, it has become easier to assess RV parameters preoperatively, allowing for a more precise risk stratification of patients. Metrics such as tricuspid annular plane systolic excursion (TAPSE), RV fractional area change, and RV strain provide valuable insights into the extent of RV dysfunction and its potential impact on surgical outcomes.[15]

Tricuspid valve surgery is a less frequently addressed and often neglected area compared to other valve surgeries. However, surgical intervention before deterioration of right ventricular function is one of the most important priorities of tricuspid valve surgery. The timing of surgery plays a decisive role in the long-term prognosis of patients.

The present study aims to investigate the specific effects of varying degrees of right ventricular dysfunction, ranging from mild to severe, on postoperative outcomes in patients undergoing cardiovascular surgery, particularly in tricuspid valve surgery. RV function was assessed using echocardiographic parameters, including TAPSE, tissue Doppler imaging (TDI), mean pulmonary artery pressure (MPAB), and valve size. Our hypothesis is that patients with severe RV dysfunction will exhibit higher mortality and reoperation rates compared to those with normal RV function. By analyzing a cohort of patients with differing levels of RV function, this study seeks to provide a clearer understanding of how RV impairment, as measured by these echocardiographic parameters and valve size, influences post-surgical prognosis and contributes to the growing body of literature highlighting the importance of RV function in cardiovascular surgeries.

2. MATERIAL AND METHODS

2.1. Study design and population

This study was a retrospective cohort analysis aimed at investigating the impact of right ventricular (RV) dysfunction on postoperative mortality and reoperation rates in patients undergoing tricuspid valve surgery. The study included 100 patients who underwent tricuspid valve replacement. Of these patients, 82 underwent sternotomy, and 18 underwent thoracotomy. Ethical approval was obtained from the 1nd Clinical Research Ethics Committee of Ankara Bilkent City Hospital on 07.06.2023, with decision number TABED-1-24-529. This study adhered to the principles outlined in the Declaration of Helsinki. All patient data were anonymized, and informed consent was obtained from all participants.

2.2. Patient selection

Patients included in this study were selected based on specific inclusion and exclusion criteria. All patients who had undergone tricuspid valve replacement and had complete preoperative

echocardiographic data available to assess RV function were included. Postoperative outcomes, such as mortality and reoperation rates, were documented. Patients with incomplete preoperative echocardiographic assessments or those who underwent surgeries unrelated to the tricuspid valve were excluded. Additionally, patients with severe left ventricular dysfunction that could interfere with the independent evaluation of RV performance were excluded from the study.

2.3. Assessment of right ventricular function

Preoperative right ventricular function was evaluated using echocardiography and classified based on three key parameters: mean pulmonary artery pressure, tricuspid annular plane systolic excursion, and tissue Doppler imaging, along with ventricular and atrial size. MPAP primarily indicates the afterload imposed on the right ventricle and does not directly measure RV function, but persistently elevated MPAP values can lead to long-term functional impairment of the RV. TAPSE is a critical marker of RV systolic function and measures the systolic motion of the tricuspid annulus. TAPSE values were used to classify RV function into four categories: normal (≥17 mm), mildly depressed (13-16 mm), moderately depressed (9-12 mm), and severely depressed (<9 mm). TDI provides a quantitative measure of myocardial velocities and was used to assess systolic and diastolic function of the RV. TDI values below 10 cm/s were considered indicative of RV dysfunction in this study. The size of the right ventricle and right atrium was also measured to evaluate ventricular and atrial enlargement, providing additional context for surgical decision-making. Based on these parameters, patients were stratified into normal, mildly depressed, moderately depressed, and severely depressed RV function groups.

2.4. Surgical procedures

All patients underwent standard tricuspid valve replacement, with the choice between bioprosthetic or mechanical valves determined by the operating surgeon based on individual patient factors. All surgeries were performed using cardiopulmonary bypass (CPB). Two distinct approaches were employed during CPB: either on a beating heart, where the heart continued to beat without cross-clamping, or on an arrested heart, where the heart was temporarily stopped using cross-clamp and myocardial protection strategies.

The choice of approach (beating heart or arrested heart) was made by the operating surgeon, considering patient-specific clinical conditions and surgical factors. In cases where an arrested heart approach was used, myocardial protection was ensured through standard techniques such as cold blood cardioplegia or intermittent cross-clamp release to minimize ischemic injury. The beating heart approach, where CPB was initiated without cardioplegia, was utilized in select cases to maintain continuous coronary perfusion. While these procedural variations were applied to accommodate individual surgical needs, they were not analyzed as separate variables in this study. Instead, this information was included to describe the technical variability inherent in tricuspid valve surgeries

2.5. Postoperative outcomes

The primary outcomes of the study were postoperative mortality and reoperation rates. Mortality was defined as any death occurring during the hospital stay or within 30 days post-surgery. Reoperations were defined as any subsequent surgical intervention required due to valve dysfunction, prosthesis failure, or other complications. Secondary outcomes included length of stay in the intensive care unit, the need for inotropic support, and the incidence of

postoperative right ventricular failure.

2.6. Statistical analysis

The data obtained from the study were transferred to the computer and organized using Microsoft Excel, and then analyzed using SPSS (Statistical Package for Social Sciences) version 29.0. Categorical data were presented with frequency and percentage values, while numerical data were expressed as means and standard deviations. The Chi-Square test was used for categorical data analysis. Since the sample size for numerical data was below 30, and the depressed levels consisted of four categories, the Kruskal-Wallis H Test, a non-parametric test, was employed for comparison of numerical variables across groups. In cases where the expected count in the Chi-Square test was below 5, Fisher's Exact Test was used. For multiple comparisons following the Kruskal-Wallis H Test, the Bonferroni post-hoc test was performed to determine which groups showed significant differences. The level of statistical significance for all tests was set at $p<0.05$.

3. RESULTS

Table 1.

Comparison of demographic, clinical characteristics, and surgical outcomes according to preoperative right ventricular function

	Normal		Mildly Depressed		Moderately Depressed		Seriously Depressed			
	$\bar{x}$±SD **Median (min-max)**		$\bar{x}$±SD **Median (min-max)**				$\bar{x}$±SD **Median (min-max)**			
Age (years)	49.11±15.36 54 (18-69)		57.54±8.65 57 (39-70)		57.13±9.98 59 (33-76)		53.45±9.41 55 (31-68)		H=5.507	0.138
	n	%	n	%	n	%	n	%	χ^2	p
Gender										
Male	6	31.6	2	15.4	12	26.7	9	45.0	3.733	0.292
Female	13	68.4	11	84.6	33	73.3	11	55.0		
Surgery Type										
Sternotomy	16	84.2	9	69.2	33	73.3	14	70.0	1.365	0.714
Thoracotomy	3	15.8	4	30.8	12	26.7	6	30.0		
Reoperation										
No	10	36.8	7	38.5	12	15.6	0	0.0	12.451	**0.006**
Yes	9	63.2	6	61.5	33	84.4	20	100.0		
Expoloration										
Re-sternotomy	9	47.4	5	38.5	19	42.2	12	60.0	5.881	0.752
Sternotomy	7	36.8	4	30.8	14	31.1	2	10.0		
Thoracotomy	2	10.5	3	23.1	8	17.8	5	25.0		
Thoracotomy (minimal)	1	5.3	1	7.7	4	8.9	1	5.0		
Valve Type										
Bioprosthesis	5	26.3	5	38.5	17	37.8	8	40.0	1.007	0.800
Metallic	14	73.7	8	61.5	28	62.2	12	60.0		

Tricuspid Regurgitation										
1TR	0	0.0	0	0.0	0	0.0	1	5.0	9.770	0.369
2TR	0	0.0	1	7.7	3	6.7	0	0.0		
3TR	3	15.8	1	7.7	9	20.0	1	5.0		
4TR	16	84.2	11	84.6	33	73.3	18	90.0		
Mortality										
Ex	0	0.0	0	0.0	10	22.2	6	30.0	8.573	**0.035**
Alive	19	100.0	13	100.0	35	77.8	14	70.0		
Need for Pace										
Yes	1	5.3	2	15.4	9	20.0	2	10.0	2.751	0.432
No	18	94.7	11	84.6	36	80.0	18	90.0		

H=Kruskal-Wallis H Test, χ^2=Chi-Square Test, p<0.05, $\bar{x}$=mean, SD=standard deviation,*Fisher Exact value was used in cases where the observation value was below 5., TR=Tricuspid regurgitation

In Table 1, the Chi-Square test was employed to assess the relationships between demographic, clinical characteristics, and surgical outcomes in relation to preoperative right ventricular function. While no statistically significant relationships were found for most variables, including age, gender, surgery type, exploration, valve type, tricuspid regurgitation, and pace requirement (p>0.05), significant differences were observed for both reoperation and mortality.

Reoperation rates differed significantly among the groups (p=0.006), with higher rates in the moderately and seriously depressed groups, where 84.4% and 100% of patients underwent reoperation, respectively. In contrast, the normal and mildly depressed groups had lower reoperation rates of 63.2% and 61.5%. Additionally, a significant difference in mortality was found between the groups (p=0.035). Mortality was observed in 22.2% of patients in the moderately depressed group and 30.0% in the seriously depressed group, while no deaths occurred in the normal and mildly depressed groups. These findings highlight the greater risk of reoperation and mortality in patients with moderate to severe right ventricular dysfunction compared to those with normal or mildly depressed function.

Table 2.

Post-hoc analysis of mortality data

Comparison Groups	**p-value**
Normal vs. Mildly Depressed	-
Normal vs. Moderately Depressed	0.032
Normal vs. Seriously Depressed	0.028
Mildly Depressed vs. Moderately Depressed	0.041
Mildly Depressed vs. Seriously Depressed	0.035
Moderately Depressed vs. Seriously Depressed	0.849

p<0.05

In table 2, the results of the Bonferroni post-hoc analysis are presented to compare the mortality rates among the different preoperative right ventricular function groups. The analysis revealed significant differences between the normal and moderately depressed groups (p=0.032), as well as between the normal and seriously depressed groups (p=0.028). Similarly, there was a significant difference between the mildly depressed group and both the moderately depressed (p=0.041) and seriously depressed (p=0.035) groups. However, no significant difference was found between the moderately depressed and seriously depressed groups (p=0.849). These results highlight that mortality rates are significantly higher in the moderately and seriously depressed groups compared to the normal and mildly depressed groups, while the mortality rates between the moderately and seriously depressed groups remain statistically similar.

Table 3.

Comparison of preoperative right ventricular function parameters (MPAB, TDI, TAPSE) and valve size measurements

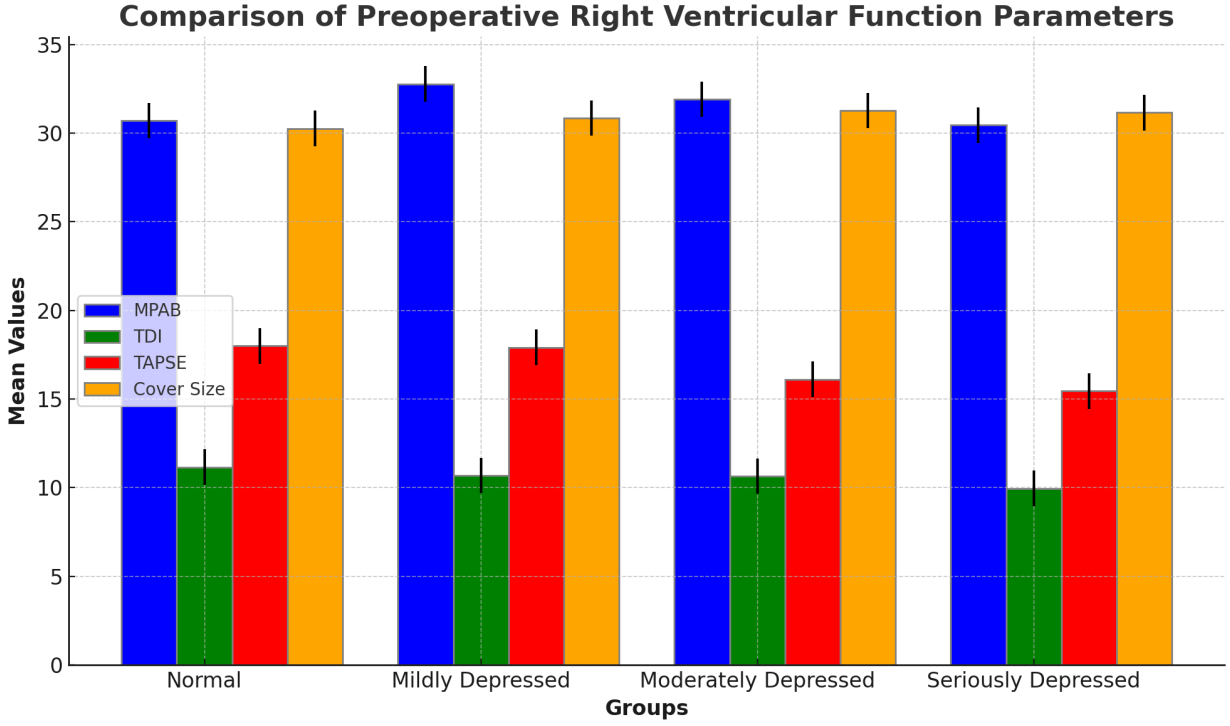
	Normal		Mildly Depressed		Moderately Depressed		Seriously Depressed			
	$\bar{x}$±SD	Median (Lover-Upper)	$\bar{x}$±SD	Median (Lover-Upper)	$\bar{x}$±SD	Median (Lover-Upper)	$\bar{x}$±SD	Median (Lover-Upper)	H	p
Preoperative MPAB	30.79±10.93	30 (14-55)	32.77±10.65	30 (20-55)	31.91±9.32	30 (15-53)	30.45±8.78	29.5 (20-44)	0.526	0.913
Preoperative TDI	11.16±3.10	11 (6-18)	10.68±2.45	11 (7-16)	10.65±2.35	10 (6.5-16)	9.96±2.04	9.65 (7.5-16)	2.496	0.476
Preoperative TAPSE	18.00±4.52	16 (14-29)	17.92±3.52	17 (13-24)	16.11±2.05	16 (13-23)	15.45±3.09	16 (10-25)	6.141	0.105
Cover size	30.26±2.02	31 (27-33)	30.85±2.23	31 (27-33)	31.27±1.51	31 (27-33)	31.15±1.39	31 (29-33)	3.601	0.308

Kruskal-Wallis H Test, p<0,05.,$\bar{x}$=mean, SD=standard deviation., Preoperative mean pulmonary artery pressure (MPAP), Tissue Doppler imaging (TDI), Tricuspid annular plane systolic excursion (TAPSE)

According to Table 3, the Kruskal-Wallis H test was used to evaluate whether there was a statistically significant difference between preoperative mean pulmonary artery pressure (MPAP), tissue Doppler imaging (TDI), tricuspid annular plane systolic excursion (TAPSE), and valve size measurements based on preoperative right ventricular function. The mean preoperative MPAP in patients with normal right ventricular function was 30.79±10.93, in mildly depressed patients it was 32.77±10.65, in moderately depressed patients it was 31.91±9.32, and in severely depressed patients it was 30.45±8.78. No statistically significant differences were observed between right ventricular function and preoperative MPAP values (p>0.05). Similarly, no significant relationships were found between preoperative TDI, TAPSE, valve size, and right ventricular function (p>0.05).

Figure 1.

Comparison of preoperative right ventricular function parameters (MPAB, TDI, TAPSE, and Valve Size) across different levels of ventricular function



The bar chart illustrates the comparison of preoperative right ventricular function parameters across four groups: Normal, Mildly Depressed, Moderately Depressed, and Seriously Depressed. The parameters include Preoperative Mean Pulmonary Artery Pressure (MPAB), Tissue Doppler Imaging (TDI), Tricuspid Annular Plane Systolic Excursion (TAPSE), and Valve Size (Cover Size). Each group is represented by distinct colored bars with error bars indicating standard deviations. The mean values for each parameter are displayed, showing no significant differences between the groups for these preoperative measurements.

The findings of this study highlight the crucial impact of right ventricular dysfunction on postoperative outcomes in patients undergoing tricuspid valve surgery. Prior research has predominantly focused on the role of left ventricular function in cardiovascular surgeries, often underestimating the significance of RV function.[13,16] However, this study confirms that RV dysfunction, particularly in its severe form, is a strong predictor of increased mortality and reoperation rates, emphasizing the need for comprehensive RV evaluation in preoperative assessments.[17,18]

Several studies in the literature support these findings.[19,20] For instance, research by Sanchez et al. demonstrated that RV dysfunction, as measured by parameters like tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (RVFAC), significantly correlates with poorer postoperative outcomes, including higher mortality rates.[21] These parameters, widely used in clinical practice, are reliable indicators of RV systolic function and were similarly applied in this study to categorize patients based on their level of RV dysfunction. Our results align with this previous research, showing that patients with severely depressed RV function had the worst postoperative outcomes, highlighting the prognostic value of RV assessment.

The pathophysiology of RV dysfunction during cardiovascular surgery, particularly when cardiopulmonary bypass is involved, has been extensively studied.[22] As reported by Mattei et al., the RV is more susceptible to ischemia-reperfusion injury due to its thinner wall and increased dependence on low afterload in the pulmonary circulation.[23] The stress placed on the RV during cardiopulmonary bypass can lead to acute dysfunction, increasing the risk of postoperative complications such as RV failure.[24] In our study, patients with preoperative RV dysfunction were more likely to experience hemodynamic instability, prolonged intensive care unit stays, and a greater need for inotropic support findings consistent with other studies that link RV dysfunction to poor postoperative recovery.[25]

Moreover, the relationship between RV dysfunction and reoperation rates is an important aspect of this study. Studies like those by Merlo et al. have found that patients with impaired RV function are more likely to require reoperation after valve surgery.[26] Our results similarly demonstrated that patients with severe RV dysfunction had significantly higher reoperation rates, indicating that RV impairment complicates the postoperative course and increases the likelihood of subsequent surgical interventions.

In addition to its effects on mortality and reoperation, RV dysfunction also influences long-term outcomes by contributing to prolonged recovery periods and increased hospital resource utilization. As noted by Scudiero et al., RV dysfunction not only affects immediate postoperative stability but can also have long-term repercussions on patient quality of life and survival. This study did not include long-term follow-up, but future research should aim to explore how RV dysfunction impacts patients beyond the initial postoperative period.[27]

This study's use of echocardiographic parameters, including TAPSE and mean pulmonary artery pressure (MPAP), provided an objective and clinically meaningful assessment of RV function. These measures are widely accepted in the literature as key indicators of RV performance, and their application in this study allowed for a clear stratification of patients into functional categories. The consistency of these parameters across studies strengthens their role in preoperative risk assessment, especially in complex cardiovascular surgeries like tricuspid valve replacement or repair.

Limitations

There are several limitations to this study that must be acknowledged. First, the retrospective nature of the study may have introduced selection bias, and the reliance on medical records may have resulted in incomplete data for some patients. Furthermore, while echocardiography is a widely used tool for assessing RV function, the addition of more advanced imaging techniques, such as cardiac MRI or 3D echocardiography, could provide a more comprehensive evaluation of RV mechanics. Finally, the lack of long-term follow-up limits our understanding of how RV dysfunction affects survival and reoperation rates beyond the immediate postoperative period. Future studies should focus on longitudinal outcomes to better understand the extended impact of RV dysfunction on patient prognosis.

4. CONCLUSION

In conclusion, this study highlights the pivotal role of right ventricular function in predicting postoperative outcomes for patients undergoing tricuspid valve surgery. RV dysfunction was found to significantly increase the risk of mortality and reoperation, especially in patients with severely depressed RV function. These findings emphasize the importance of timely surgical

intervention before significant RV dysfunction develops, aligning with existing literature that underscores the prognostic value of RV function in cardiovascular surgeries. Careful preoperative evaluation, including the use of echocardiographic parameters such as TAPSE, TDI, and MPAP, is essential for optimizing patient outcomes. As RV dysfunction remains a critical determinant of postoperative success, further research is needed to investigate advanced diagnostic tools and long-term outcomes to enhance patient care and refine surgical strategies.

Declarations

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Competing Interests:
The authors declare no competing interests.

Authors Contributions:
All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Muhammet Fethi Sağlam, Emrah Uguz, Kemal Eşref Erdoğan, Hüseyin Ünsal Erçelik, Murat Yücel, Mete Hıdıroğlu, and Erol Şener. The first draft of the manuscript was written by Muhammet Fethi Sağlam, Emrah Uguz, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval:
This study received ethical approval from the 1nd Clinical Research Ethics Committee of Ankara Bilkent City Hospital on 07.06.2023, with decision number TABED-1-24-529. The study, was reviewed and unanimously approved in terms of ethical considerations.

Consent to Participate:
Informed consent was obtained from all individual participants included in the study.

Availability of Data and Materials:
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Research Article

Evaluation of the Anti-Cancer Effect of TRAF2 and NCK Interacting Protein Kinase (TNIK) Inhibition in Breast Cancer Cells

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Objective: This study aimed to evaluate the anticancer effect of NCB-0846, a TNIK inhibitor, in MCF-7 cells and to assess its impact on the expression levels of NF-κB and TNFA at the gene level.

Materials and Methods: The MCF-7 cell line was cultured at 37°C in a 5% CO2 atmosphere using Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and antibiotics (50 IU/mL penicillin and 50 mg/mL streptomycin). Cell viability was analyzed using the CCK-8 assay to determine the cytotoxic effect of NCB-0846. Acridine Orange/Propidium Iodide (AO/PI) staining was performed to evaluate the effect of NCB-0846 on cellular morphology in the MCF-7 cell line. Total RNA was isolated from cells treated with NCB-0846. Data analysis was performed using the SPSS 22.0 statistical program.

Results: The data indicated that NCB-0846 significantly decreased the viability rates of MCF-7 cells in a dose-dependent manner (1-3 μM, $p<0.01$). RT-PCR analysis revealed that the expression level of NFKB1 increased 5.4-fold compared to the control group in MCF-7 cells treated with NCB-0846 at the effective dose and duration ($p<0.01$). In contrast, the expression level of TNFA decreased to 0.4-fold compared to the control group ($p<0.01$).

Conclusion: The results demonstrate that NCB-0846 induces changes in the mRNA levels of the NFKB1 and TNFA genes, which are associated with inflammatory signalling pathways in MCF-7 cells. However, further molecular analyses are necessary to clarify the effect of NCB-0846 on inflammation in breast cancer and other cancer types.

Keywords: Breast cancer, Inflammation, NCB-0846, TNIK

1. INTRODUCTION

Breast cancer is one of the most common cancers among women and is a leading cause of death.[1] The Luminal A breast cancer subtype is positive for estrogen receptors (ER) and progesterone receptors (PR), and negative for human epidermal growth factor receptor 2 (HER2).[2] The Luminal A breast cancer subtype, which represents over half of all breast cancer cases, is characterized by a better prognosis and less aggressive features compared to other subtypes. However, challenges such as resistance to hormonal treatment, the formation of cancer stem cells, and systemic toxicity can limit the effectiveness of current treatment options.[3-6] Therefore, there is a pressing need to develop innovative treatment strategies.

TNIK, or TRAF2 Nck-interacting protein kinase, is a serine/threonine kinase that belongs to the germinal center kinase (GCK) family. Members of the GCK family are subgroups within the STE20 kinase family, and they interact with two key proteins: tumour necrosis factor (TNF) receptor-associated factor 2 (TRAF2) and NCK adaptor protein 1 (NCK1). The TNIK molecule plays a crucial role in regulating the nuclear factor-κB

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(NF-κB) signaling pathway through its N-terminal kinase domain, as well as the c-JUN N-terminal kinase (JNK) pathway via its C-terminus.[7-9] The TNIK protein is a key molecular regulator in the Wnt signaling pathway, which is known to have varying activity levels in many cancers, including breast cancer. This pathway plays a crucial role in regulating various cellular processes, such as cell growth and differentiation.[10] The TNIK molecule plays a crucial role in the transcription of Wnt target genes by facilitating the interaction between T cell factor 4 (TCF-4), a member of the TCF/LEF transcription factor family, and β-catenin.[11] Due to its significant properties, TNIK presents a potential therapeutic target for various types of cancer, particularly breast cancer. The compound NCB-0846, known as cis-4-(2-(3H-benzo[d]imidazol-5-ylamino)quinazolin-8-yloxy) cyclohexanol, is a small molecule TNIK inhibitor that demonstrates inhibitory activity against TNIK, with a half-maximum inhibitory concentration (IC50) of 21 nM.[12,13] Studies have reported the efficacy of NCB-0846 across various cancer types, including colorectal, lung, breast, and prostate, demonstrating promising effects in suppressing Wnt-mediated tumor formation, reducing cancer stem cells, and inhibiting epithelial-mesenchymal transition (EMT).[14-22] The interaction of TNIK with TRAF2 also contributes to the activation of specific cytokine receptors, particularly tumor necrosis factor alpha (TNF-α). TNF-α is a critical cytokine that regulates apoptosis, cell survival, and inflammatory responses. It binds to two types of receptors: TNFR1 and TNFR2, triggering different molecular signaling pathways. When TNF-α interacts with TNFR1, the TRAF2 molecule acts as a mediator in its interaction with TNF receptor-associated death domain protein (TRADD). While TRADD can induce apoptosis through FADD, it simultaneously activates the NF-κB pathway, which has various effects, including inflammation and cell survival, by stimulating IκB kinases (IKK).[23-25] The NF-κB family comprises multiple transcription factors, including RelA, RelB, c-Rel, NF-κB1/p50, and NF-κB2/p52. These transcription factors remain inactive in the absence of signals and are located in the cytoplasm, bound by IκB proteins. Upon receiving a signal, the degradation of IκB facilitates the translocation of NF-κB transcription factors into the nucleus, leading to the production of pro-inflammatory molecules such as cytokines, chemokines, Bcl-XL, vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP)-2, and MMP-9 in tumor cells. NF-κB plays a crucial role in cancer progression due to its dual function in regulating both apoptosis and cell survival.[23,26,27]

This study investigates, for the first time, the anticancer effects of NCB-0846, a TNIK inhibitor, in MCF-7 breast cancer cells. Additionally, it examines the impact of NCB-0846 on the TNF-α and NF-κB signaling pathways, which play crucial roles in inflammation and cell survival, at the gene level.

2. METHODOLOGY

2.1. Ethics committee approval

This study utilized commercially available cell cultures. Approval from an ethics committee is not required.

2.2. Cell culture

The MCF-7 cell line was grown at 37°C in an atmosphere with 5% CO2. The culture medium used was Dulbecco's Modified Eagle Medium (DMEM), which was supplemented with 10% fetal bovine serum (FBS) and contained 50 IU/mL of penicillin, along with 50 mg/mL of streptomycin.

2.3. Cell viability analysis

Cell viability was assessed using the CCK-8 assay to determine the cytotoxic effect of NCB-0846. MCF-7 cells were seeded in 96-well plates at a density of 20,000 cells per mL. NCB-0846 was

added at varying concentrations ranging from 1 to 10 μM, and the cells were incubated for either 24 or 48 hours. After the incubation period, 10 μL of CCK-8 dye was added to each well, and the plates were incubated for an additional hour at 37°C. The absorbance was then measured at 450 nm using an ELISA reader.

2.4. Acridine Orange/Propidium Iodide (AO/PI) staining

AO/PI staining was conducted to assess the impact of NCB-0846 on cellular morphology in the MCF-7 cell line. Cells were seeded at a density of 100,000 cells per mL in each well of a 6-well plate and incubated with 3 μM of NCB-0846 for 24 hours. After incubation, the cells were fixed with 4% paraformaldehyde, and acridine orange/propidium iodide (AO/PI) dye was added. The cells were then incubated in the dark for 30 minutes before imaging using the EVOS FL Cell Imaging System (Thermo Fisher Scientific).

2.5. RT-PCR analysis

To evaluate the changes in the expression levels of the NF-κB and TNF-α genes, cells were seeded at a concentration of 1,000,000 cells per mL in flasks. Total RNA was isolated from cells treated with 3 μM NCB-0846 for 24 hours. The quantity and purity of the isolated RNA were assessed using a Qubit device (Invitrogen). cDNA synthesis was performed on the obtained RNA, followed by RT-PCR analysis. Beta-actin was used as a control gene.

2.6. Statistical analysis

Data analysis was performed using the SPSS 22.0 statistical software, with a significance level set at $p < 0.05$. One-way ANOVA (Post-hoch Tukey) was employed to evaluate differences in cell viability percentages. Additionally, the CT values obtained from the RT-PCR analysis were presented as fold changes using the "REST (2009 V2.0.13)" software.

3. RESULTS

3.1. Evaluation of the anti-cancer effect of TNIK inhibition

A CCK-8 cell viability analysis was conducted to evaluate the cytotoxic effects of the TNIK inhibitor NCB-0846 on MCF-7 breast cancer cells. The data presented in Figure 1 indicate that cell viability in MCF-7 cells treated with 1, 2, 3, 4, 6, 8, and 10 μM of NCB-0846 for 24 hours was measured at 63.9±0.1%, 57±2.2%, 54.4±0.2%, 56.5±1.5%, 52.9±0.5%, 59.9±0.2%, and 63.7±0.2%, respectively ($p<0.01$). Following treatment with the same concentrations for 48 hours, the viability of MCF-7 cells was assessed at 33.3±2.9%, 26.1±1.7%, 24.7±2.3%, 26.6±2.6%, 25.5±1.6%, 24.9±1%, and 24.1±0.8%, respectively. This demonstrates an increased cytotoxic effect of TNIK inhibition over the 24-hour treatment period ($p<0.01$). Based on the results from the CCK-8 analysis, a 3 μM dose of NCB-0846 was subsequently applied to the cells for 24 hours in further molecular analyses (Figure 1).

3.2. Evaluation of the effect of TNIK inhibition on cell morphology

The morphological changes in MCF-7 cells after TNIK inhibition were evaluated using AO/PI staining. It was observed that breast cancer cells treated with 3 μM NCB-0846 for 24 hours showed signs of late apoptotic death when compared to the control cells (see Figure 2).

Furthermore, TNIK inhibition resulted in the formation of numerous vacuoles within the MCF-7 cells (Figure 2).

3.3. Effect of TNIK inhibition on gene expression levels

RT-PCR analysis was conducted to quantitatively evaluate the effects of NCB-0846 on the mRNA levels of NFKB1 and TNFA in MCF-7 cells. The results are presented in Figure 3. The analysis

revealed that TNFA expression decreased by 0.4-fold, while the mRNA level of NFKB1 increased by 5.4-fold. Both changes were statistically significant in breast cancer cells treated with 3 µM of NCB-0846 for 24 hours, compared to control cells ($p < 0.01$) (Figure 3).

Figure 1.

*Dose-dependent viability analysis results in MCF-7 cells treated with NCB-0846 (p<0.01**)*

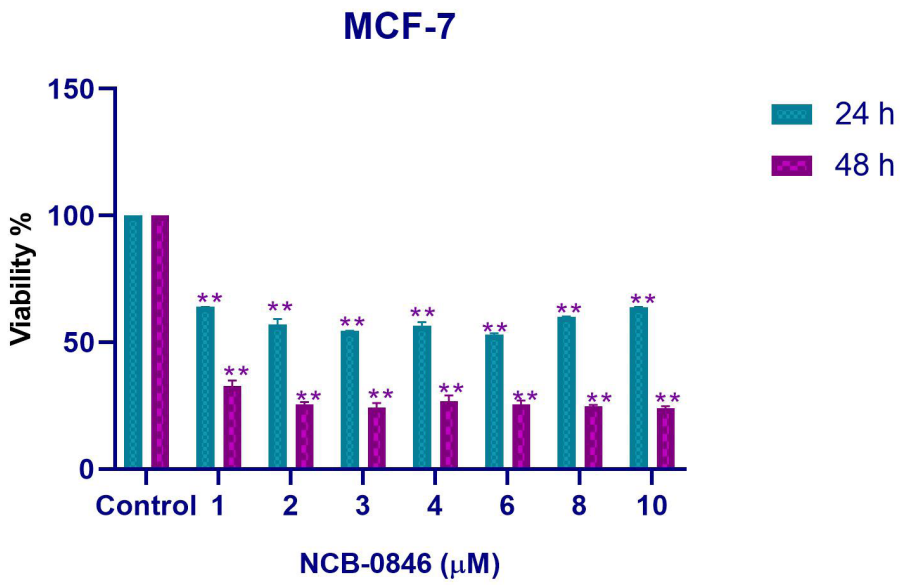


Figure 2.

AO/PI images in MCF-7 cells after NCB-0846 application. (A) Control (B) Cells treated with 3 µM NCB-0846 for 24 hours

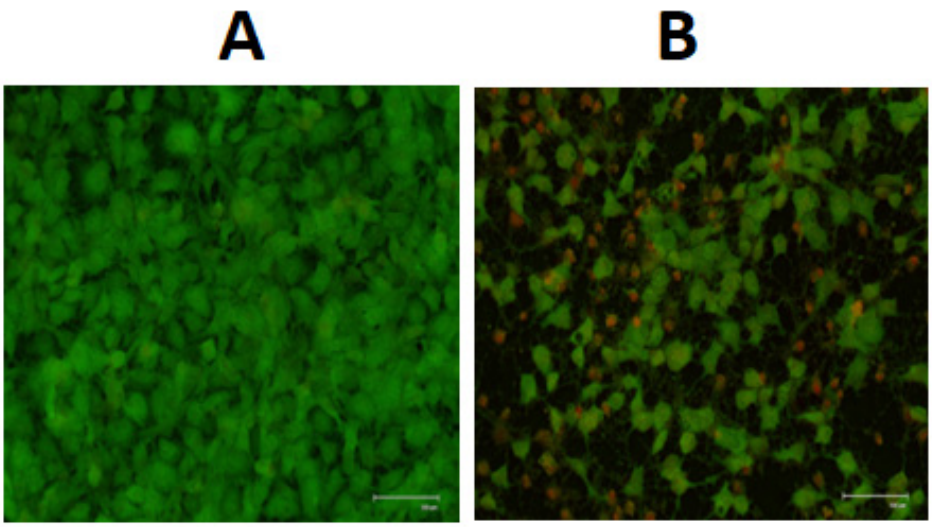
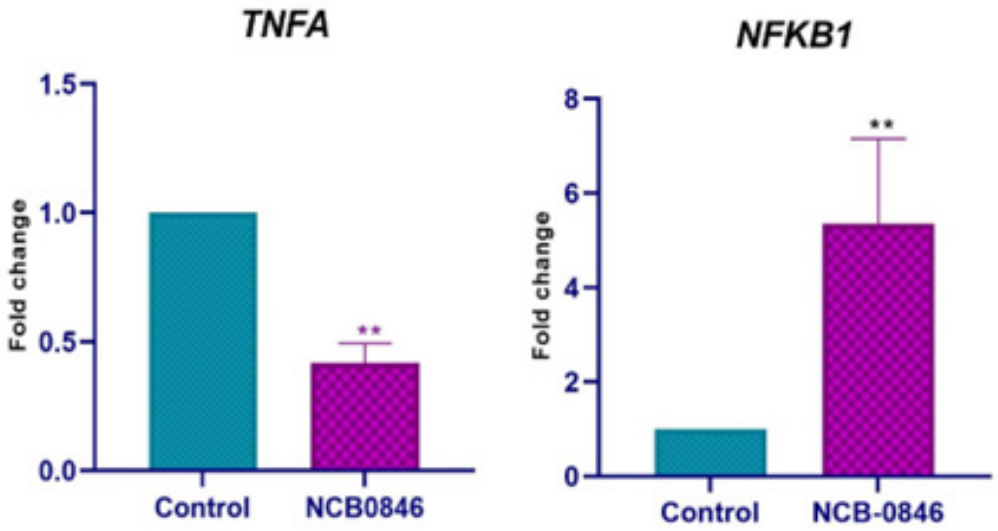


Figure 3.

*RT-PCR analysis results of NFKB1 and TNFA expression levels in MCF-7 cells treated with NCB-0846 (p<0.01**)*



4. DISCUSSION

This study is the first to investigate the anti-cancer effects of TNIK inhibition mediated by NCB-0846 in MCF-7 breast cancer cells. The data demonstrate that inhibiting TNIK results in a reduction of cell viability in MCF-7 cells, as well as the induction of apoptosis and the formation of multiple vacuoles. Furthermore, we observed an increase in the expression level of NFKB1 in MCF-7 cells treated with NCB-0846. These findings provide the first preclinical evidence suggesting that TNIK inhibition may be a potential therapeutic target for MCF-7 breast cancer cells.

Numerous studies in the literature have explored the therapeutic effects of TNIK inhibition as a potential treatment strategy for various types of cancer. [14-22] For example, a study conducted by Masuda et al. found that NCB-0846 exhibited anti-cancer effects both in vitro and in vivo by suppressing the Wnt signaling pathway in colorectal cancer (CRC). This compound demonstrated cytotoxic effects on CRC cells and stem cells, inducing apoptosis by increasing the sub-G1 cell population. Additionally, the study reported that NCB-0846 reduced tumor growth in animal models by inhibiting TCF/LEF activity in CRC. Alongside TNIK/Wnt inhibition, it also suppressed the expression of proteins such as CDK2/CycA2, JAK3, PDGFRα, and various mesenchymal biomarkers involved in different signaling pathways.[14] In a more recent study by Zhang et al., the anti-cancer efficacy of TNIK inhibition was investigated in papillary thyroid carcinoma (PTCa).[17] The findings demonstrated that NCB-0846, functioning as a TNIK inhibitor, significantly suppressed TNIK kinase activity in different PTC cell lines (TPC-1, KTC-1, and BCPAP). It induced apoptosis through the activation of apoptosis-related proteins and inhibited tumor growth in an in vivo PTC mouse model.[17] Additionally, several studies have shown that different TNIK inhibitors, particularly NCB-0846, exhibit anti-metastatic efficacy by suppressing the TGF-β1/SMAD-mediated epithelial-mesenchymal transition (EMT) in lung adenocarcinoma.[27-29] Sato et al. conducted a study on triple-negative breast cancer (TNBC) and revealed that 108600-mediated TNIK inhibition reduced colony formation and cell

growth in breast cancer stem cell-like cells. This inhibition induced apoptosis by causing cell cycle arrest in the G2/M phase and helped overcome chemotherapy resistance in an in vivo model.[29] Despite highlighting the therapeutic efficacy of TNIK inhibitors across various cancer types, research on the effectiveness of different TNIK inhibitors, particularly NCB-0846, in breast cancer remains limited. In the current study, NCB-0846 demonstrated cytotoxic and late apoptotic effects on MCF-7 Luminal A-type breast cancer cells. Its anti-cancer efficacy was confirmed; however, further studies are warranted to investigate the numerous vacuoles observed in cells treated with NCB-0846.

NF-κB is a critical transcription factor that regulates the expression of genes involved in various cellular processes, including inflammation, cell death, and proliferation. It is regulated by the N-terminal kinase domain of TNIK and the c-Jun N-terminal kinase (JNK) signalling pathway.[30] NF-κB significantly influences the expression of inflammatory genes, such as TNF-α, IL-1β, IL-6, IL-12p40, and COX2, particularly in cancer and immune cells. Notably, TNF-α and IL-1β are recognized activators of NF-κB, which shows a strong correlation with NF-κB expression.[31] Our study indicates that inhibiting TNIK leads to an increase in NFKB1 expression in MCF-7 cells while decreasing TNFA mRNA levels. Therefore, there is a need for advanced molecular analyses to explore other NF-κB-related inflammatory pathways and cytokine expressions as alternatives to the NF-κB/TNF-α-mediated signaling pathway associated with TNIK inhibition in breast cancer cells. The cytoskeleton is a dynamic system composed of actin filaments, intermediate filaments, and microtubules. These components can bind to one another or attach to various membrane compartments, forming organized structures. Modulating the cytoskeleton is essential for facilitating vacuole formation, as well as for processes like epithelial-mesenchymal transition (EMT) and metastasis in cancer cells.[32] Literature highlights the direct effects of TNIK on cytoskeleton remodelling, particularly regarding the actin cytoskeleton, as well as its indirect influence through the Wnt/β-catenin pathway.[33,34] Additionally, AO/PI staining results showed that TNIK inhibition with NCB-0846 in MCF-7 cells resulted in vacuole formation. To better understand the anti-cancer efficacy of TNIK inhibitors across different cancer types, especially breast cancer, further preclinical studies are needed to investigate the effects of TNIK inhibition on non-apoptotic cell death mechanisms associated with vacuole formation as an alternative to apoptosis.

In conclusion, this study demonstrates, for the first time, the anti-cancer activity of NCB-0846 as a TNIK inhibitor in MCF-7 breast cancer cells. We have also revealed, for the first time, the relationship between NCB-0846 and inflammation. However, further molecular analyses are required to explore the findings we obtained across different breast cancer cell lines. Additionally, future studies could investigate the NF-κB signalling pathway and related cytokines in MCF-7 cells treated with NCB-0846.

Ethics Committee Approval:
This study was conducted using commercially available cell cultures. Ethics committee approval is not required.

Author Contributions:
SZO and KFH conceptualized the study. SZO, KFH, and GGE designed the study. SZO, KFH, and GGE were responsible for data collection. GGT conducted the statistical analysis. SZO, KFH, and GGE prepared the draft manuscript, while GGE and SK finalized the manuscript.

Conflict of Interest:

All authors declare no conflict of interest.

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Research Article/ Araştırma Makalesi

Hipertansiyon Hastalarının Yaşam Tarzı Değişikliklerine ve İlaç Tedavisine Uyumlarının incelenmesi

Examining the Compliance of Hypertension Patients with Lifestyle Changes and Medication Therapy

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Amaç: Hipertansiyon günlük hayatta her hekimin karşılaşabildiği, morbiditesi ve mortalitesi yüksek, günümüz dünyasının en önemli hastalıklarından bir tanesidir. Çalışmamızda hipertansif hastaların yaşam tarzı değişikliklerine (YTD) uyum düzeylerinin ve ilaç tedavisi uyumlarının belirlenmesi ve bunları etkileyen faktörlerin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamıza 1 Nisan- 30 Haziran 2023 tarihleri arasında bir eğitim ve araştırma hastanesi aile hekimliği kliniğine bağlı poliklinikler ve aile hekimliği kliniğine bağlı bir eğitim aile sağlık merkezine başvuran 351 hasta dahil edildi. Bu hastalara araştırmacılar tarafından hazırlanmış sosyodemografik verilerin, hastalığına ait genel bilgilerin ve YTD önerilerine uyumun değerlendirildiği soruların bulunduğu 31 soruluk bir anket ve Morisky 8 Maddeli İlaç Uyum Ölçeği uygulanmıştır.

Bulgular: Çalışmamızda hastaların %85,2'sinin hipertansiyon tanısı aldığında doktoru tarafından YTD önerileri hakkında bilgilendirildiği, bilgilendirilen hastaların; tuz alımlarında ve kilolarında azalma olduğu, fiziksel aktivitelerinde artış gözlendiği, beslenme alışkanlıkların düzelmesinde istatiksel olarak anlamlı düzeyde yüksek bulunmuştur. Kırsal bölgede yaşayan hastaların kentsel bölgede yaşayanlara göre, evde tansiyon aleti bulunduranlarda bulundurmayanlara göre, tansiyonlarını düzenli ve bazen ölçenlerde düzenli ölçmeyenlere göre, kontrollere düzenli olarak giden hastalarda kontrollere düzenli olarak gitmeyen hastalara göre, günlük tuz alımları 5-6 gr'dan az olan hastaların kullanımı fazla olanlara göre tedavi uyumu istatistiksel olarak anlamlı düzeyde yüksek tespit edilmiştir.

Sonuç: Hipertansiyon tanılı hastalara YTD'nin anlatılması ve bu değişikliklerin hayata geçirilmesi konusunda desteklenmeleri, YTD'nin içselleştirilmesine ve ilaç uyumunun artmasına katkıda bulunacağını düşünmekteyiz.

Anahtar Kelimeler: Hipertansiyon, Sağlıklı yaşam tarzı, Tedavi uyumu

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Objective: Hypertension is one of the most important diseases in today's world, which every physician can encounter in daily life, with high morbidity and mortality. In this study, it was aimed to determine the level of compliance with lifestyle changes and drug treatment compliance in hypertensive patients and to investigate the factors affecting them.

Materials and Methods: A total of 351 patients who visited the family medicine clinics affiliated with a training and research hospital and a training family health center connected to the family medicine clinic between April 1 and June 30, 2023, were included in our study. A 31-item questionnaire and Morisky 8-item Medication Compliance Scale were applied to the patients, which included sociodemographic data prepared by the researchers, general information about the disease, and questions about compliance with lifestyle change recommendations.

Results: In our study, 85.2% of the patients were informed about the lifestyle change recommendations by their doctor when they were diagnosed with hypertension; It was found that there was a decrease in salt intake and weight, an increase in physical activities, and a positive increase in eating habits were found to be statistically significantly high. The daily salt intake is less than 5-6 g in patients who live in a rural area compared to patients in an urban area, those who have a sphygmomanometer at home compared to those who do not have a blood pressure monitor at home, those who regularly and sometimes measure their blood pressure compared to those who do not regularly measure their blood pressure, and those who regularly go to the controls compared to the patients who do not regularly go to the controls. Compliance with treatment was found to be statistically significantly higher in patients with high blood pressure.

Conclusion: We think that explaining lifestyle changes to patients with hypertension and supporting them in implementing these changes will contribute to the internalization of lifestyle changes and increase drug compliance.

Keywords: Hypertension, Healthy lifestyle, Medication adherence

EXTENDED ABSTRACT

Introduction: The global increase in life expectancy and the widespread prevalence of unhealthy living conditions have led to a rise in chronic diseases, particularly hypertension. Hypertension is a significant risk factor for serious health issues such as coronary artery disease, heart failure, kidney failure, and stroke. In the United States, one in three adults has hypertension, and the lifetime risk of developing hypertension for individuals over 55 is 90%. According to the TURDEP-II study, the prevalence of hypertension in Turkey is 31.3%.

The treatment of hypertension involves both lifestyle changes (such as quitting smoking, reducing alcohol intake, engaging in regular exercise, healthy eating, avoiding stress, and reducing salt intake) and medication. However, patients often overlook lifestyle changes and focus solely on medication. The success of treatment depends on the patient's adherence to the prescribed regimen. This study aims to identify the factors affecting the adherence of hypertension patients to lifestyle changes and medical treatment.

Material and Methods: This descriptive and cross-sectional study included 351 patients who applied to the family medicine clinics of an educational and research hospital and an affiliated educational family health center between April 1 and June 30, 2023.

The questionnaire used in the study consists of 31 questions prepared by the authors and the 8-item Morisky Medication Adherence Scale. The first 11 questions of the survey inquire about sociodemographic characteristics. The second section addresses the duration of hypertension

diagnosis, the presence of other chronic diseases, the development of complications related to hypertension, the presence of a blood pressure measuring device, and blood pressure measurement habits. The third section investigates the initial healthcare center visited for any health problem, the annual number of visits to the family physician, the healthcare center visited for hypertension-related problems and the reason for visiting this center, regular follow-ups for hypertension monitoring, and the reasons for not attending these follow-ups. The fourth section evaluates the implementation of the recommended lifestyle changes (LSC) by patients diagnosed with hypertension. The final section assesses patients' adherence to medication treatment using the 8-item Morisky Medication Adherence Scale.

Results: A total of 351 hypertensive patients participated in our study, of which 228 were women. The average age was found to be 60.4±10.8 years (min=24.0, max=90.0). The average height was 164.1±8.2 cm (min=147.0, max=188.0), the average weight was 82.5±13.6 kg (min=46.0, max=150.0), and the average BMI was 30.7±5.2 kg/m2 (min=16.9, max=49.3). The average duration of hypertension was found to be 10.8±7.9 years (min=1.0, max=40.0). According to the Morisky Medication Adherence Scale, 28.0% (n=98) of the patients had low adherence, 24.0% (n=83) had moderate adherence, and 48.0% (n=170) had high adherence to treatment. It was found that 85.2% of the patients were informed by their doctors about LSC recommendations when diagnosed with hypertension. Among these informed patients, a statistically significant reduction was observed in their salt intake (p=0.003) and weight (p=0.002), an increase in physical activity (p=0.012), and a positive improvement in eating habits (p=0.000). It was determined that treatment adherence was statistically significantly higher in patients living in rural areas compared to those living in urban areas (p=0.009), in those who had a blood pressure measuring device at home compared to those who did not (p=0.006), in those who measured their blood pressure regularly or sometimes compared to those who did not measure it regularly (p=0.001), in those who regularly attended follow-ups compared to those who did not (p=0.005), and in those whose daily salt intake was less than 5-6 grams compared to those with higher intake (p=0.045).

Discussion: In our study, when evaluating the adherence levels of hypertensive patients to evidence-based lifestyle changes (LSC) recommended to them, it was found that the majority did not sufficiently adhere to these recommendations. However, their adherence to medication therapy was better compared to LSC. Additionally, a positive significant relationship was found between adherence to medication therapy and adherence to lifestyle recommendations. It was determined that men adhered to LSC more than women, younger individuals more than older individuals, and those with a higher education level more than those with a lower education level. On the contrary, it was observed that women adhered to medication therapy more than men, older individuals more than younger individuals, and those with a lower education level more than those with a higher education level, although this difference was not statistically significant. Adherence to both LSC and medication therapy was found to be higher in married individuals compared to single individuals.

In our study, it was determined that patients who were informed about LSC showed an increase in physical activity after being diagnosed with hypertension compared to those who were not informed. In a study conducted in South Korea with 3802 patients, it was found that hypertensive

patients adhered to the recommended physical activities at a rate of 46%. A study conducted in our country examined the exercise habits of participants and found that 55.3% of the participants did not exercise at all, while 26.7% exercised for at least 30 minutes, three or more days a week. We believe that it would be beneficial to recommend hypertensive patients to increase their physical activities and avoid a sedentary lifestyle at each follow-up examination.

Our study found that patients who were informed about LSC positively changed their eating habits after being diagnosed with hypertension compared to those who were not informed. A study involving coronary artery disease patients showed that after being educated, the patients' knowledge level about eating habits increased, which paralleled an increase in dietary adherence and a significant decrease in blood pressure levels. These studies support our findings, and we believe it would be beneficial to provide information about nutrition to hypertensive patients, remind them at each examination, and refer them to relevant units if necessary.

Less than half of the patients showed high adherence to medication therapy. In the literature, there are many studies conducted in various populations evaluating the adherence of hypertensive patients to medication therapy, and differences in results are observed among these studies. In our study, the rate of high adherence to medication therapy was found to be 48%. It is thought that these differences in the literature may vary depending on the population studied. We believe that more comprehensive research is needed to better understand this variability.

Conclusion: In the treatment of hypertension, LSC are as important as medical therapy. The first step of the hypertension treatment plan includes LSC. In our study, it was observed that patients who implemented LSC had higher adherence to medication therapy, although the number of patients applying such interventions was found to be quite low. Despite doctors regulating medication therapies, patients' non-adherence to treatment makes it difficult to control blood pressure. Patients should be supported in understanding and implementing LSC, and programs should be developed to ensure they attend regular doctor check-ups.

1. GİRİŞ

Dünya genelinde ve ülkemizde, beklenen yaşam süresinin uzaması ve sağlıksız yaşam koşullarının yaygınlaşması, kronik hastalıkların artmasına yol açmaktadır. Hipertansiyon, önlenebilir ve kontrol edilebilir bir kronik hastalık olmasına rağmen, halen önemli bir morbidite ve mortalite sebebi olarak öne çıkmaktadır.[1-2]

Hipertansiyon, koroner arter hastalığı, kalp yetmezliği, böbrek yetmezliği ve inme için önemli bağımsız bir risk faktörüdür. Her 3 Amerikalı yetişkinden biri hipertansiyona sahiptir. 55 yaşın üzerindeki bir kişide yaşam boyu hipertansiyon gelişme riski %90'dır.[3] 2010 yılında yapılan Türkiye Diyabet, Hipertansiyon, Obezite ve Endokrinolojik Hastalıklar Prevalans Çalışması-II (TURDEP-II) verilerine göre hipertansiyonun Türkiye'deki prevalansı %31,3 olarak bulunmuştur.[4]

Hipertansiyon tedavisi geniş bir kapsamda ele alınmakta olup, hastaların yaşamlarında önemli değişiklikler yapmalarını gerektirir. Bu nedenle uygulanması genellikle zorlayıcı olabilir. Kan basıncının kontrol altına alınmasında yaşam tarzı değişiklikleri (YTD) (sigarayı bırakma, alkol alımını azaltma, düzenli egzersiz yapma, sağlıklı beslenme, stresten uzak durma, tuz tüketimini azaltma) ve ilaç tedavisi birlikte kullanılmaktadır.[5] Ancak hastalar çoğu zaman YTD'yi göz ardı ederek

ilaç tedavisine odaklanmaktadır. Bununla birlikte, ilaç tedavisinin de uygulanması kendi içinde zorluklar barındırmaktadır.[6]

Hipertansiyon tedavisinin başarılı olabilmesi, hastanın tedavi sürecine uyum sağlamasına bağlıdır. Bu uyum, sağlık profesyonellerinin önerilerine uygun olarak düzenli doktor kontrollerine gitmek, YTD'yi benimsemek ve ilaçları doğru şekilde kullanmakla mümkün olur.[7]

Çalışmamızda, hipertansiyon hastalarına sağlık profesyonelleri tarafından verilen öneril doğrultusunda YTD'ye uyumun ve bu YTD ile tıbbi tedaviye uyum arasındaki ilişkinin incelenmesi amaçlanmaktadır.

2. GEREÇ VE YÖNTEMLER

Tanımlayıcı ve kesitsel nitelikteki bu çalışma xxx Üniversitesi Eğitim ve Araştırma Hastanesi Aile Hekimliği Kliniği'ne bağlı poliklinikler ve kliniğimize bağlı xxx Eğitim Aile Sağlık Merkezi'ne başvuran hastalar ile 01/04/2023-30/06/2023 tarihleri arasında yapılmıştır.

Çalışmamız, herhangi bir nedenle ayaktan başvuran, en az 1 yıldır antihipertansif ilaç tedavisi alan, iletişim engeli olmayan ve araştırmayı kabul eden 18 yaş ve üzerindeki 351 hastaya yüz yüze görüşme ile anket uygulanarak yapılmıştır.

Yazarlar tarafından gerekli literatürler taranarak iki uzman hekim tarafından hazırlanarak oluşturulmuş 31 soruluk anket formu ve 8 sorudan oluşan Morisky 8 maddeli ilaca uyum ölçeği kullanılmıştır. Hazırlanan anket formunda ilk 11 soruluk bölümde katılımcıların yaş, cinsiyet, medeni durum, aile yapısı, eğitim düzeyi, çalışma durumu, ekonomik durumu, nerede yaşadığı, sigara alkol kullanma durumları, boy ve kilosu gibi sosyodemografik özellikler sorgulanmıştır. İkinci bölümde hipertansiyon tanı süresi, kronik bir hastalıklarının olup olmadığı, hipertansiyona bağlı komplikasyon gelişip gelişmediği, tansiyon ölçüm aletinin varlığı ve tansiyonlarını ölçme durumu sorgulanmıştır. Üçüncü bölümde herhangi bir sağlık probleminde ilk başvurduğu merkez, aile hekimine yıllık başvuru sayısı, hipertansiyon ile ilgili probleminde başvurduğu merkez ve bu merkeze başvuru nedeni, hipertansiyon takibi için kontrollere düzenli başvurma durumu ve başvuru yapmıyorsa nedeni sorulmuştur. Dördüncü kısımda hipertansiyon tanılı hastalarda önerilen YTD'nin uygulama durumları sorgulanmıştır.

Son kısımda hipertansiyon hastalığında ilaç uyumunun değerlendirilmesi için Morisky 8 Maddeli İlaç Uyum Ölçeği sorularına geçilmiştir.[8] Hastanın yanıtlarına dayanan bu ölçek, ilaç uyumunu belirlemek amacıyla 8 sorudan oluşmaktadır. Bu ölçek, ilaç tedavisine uyumu etkileyen olası nedenleri belirlemeye yardımcı olmayı amaçlamaktadır. Ölçek puanlama skalası 0-8 aralığında yer almaktadır. Toplam puan, ilaç uyumunu değerlendirmek için kullanılır ve 8 puan yüksek uyumu, 6 veya 7 puan orta uyumu, 5 puan ve altı düşük uyumu ifade etmektedir.

Etik Komite Onayı:

xxx üniversitesi girişimsel olmayan etik kurulu tarafından 15/03/2023 tarih E-71522473-050.01.04-230910-96 sayı ile tez konusu olarak onay alınmıştır.

Çalışma gönüllü onam formu doldurtulan 351 katılımcı üzerinden gerçekleştirilmiştir. Çalışmada elde edilen veriler bilgisayar ortamında IBM SPSS (sürüm 21,0) paket programı kullanılarak değerlendirilmiştir. Araştırmada tanımlayıcı istatistikler sayı (n), yüzde (%), ortalama ve standart sapma (SS) kullanılarak gösterilmiştir. Sürekli değişkenlerin normal dağılıma uygunluğu görsel yöntemlerle ve Kolmogorov Smirnov / Shapiro Wilk testleri kullanılarak değerlendirilmiştir.

Çalışmada kategorik değişkenlerin arasında fark olup olmadığını değerlendirmek için Ki Kare Testi kullanılmıştır. Bağımsız gruplarda sürekli değişkenlerin parametrik özellikleri taşımayanların karşılaştırılmasında Mann Whitney U Testi veya Kruskal Wallis Varyans Analizi kullanılmıştır. İstatistiksel anlamlılık düzeyi olarak p değerinin 0,05'ten küçük olması kabul edilmiştir.

3. BULGULAR

Çalışmamıza 228'i (%65,0) kadın toplam 351 hipertansiyon hastası katılmıştır. Yaş ortalaması 60,4±10,8 yıl (min=24,0, maks=90,0) bulunmuştur. Boy ortalaması 164,1±8,2 cm (min=147,0, maks=188,0), kilo ortalaması 82,5±13,6 kg (min=46,0, maks=150,0), VKİ ortalaması 30,7±5,2 kg/m^2 (min=16,9, maks=49,3) saptanmıştır. Evli olan katılımcılar toplam katılımcıların %79,8'ini (n=280), ilkokul ve ortaokul mezunu katılımcılar ise %58,1'ini (n=204) oluşturmaktadır. Katılımcıların %54,4'ü (n=191) ev hanıdır.

Hastaların hipertansiyon hastalığı süresi ortalaması 10,8±7,9 yıl (min=1,0, maks=40,0) yıl bulunmuştur. Hastaların %75,6'sında (n=264) hipertansiyon dışında kronik hastalığın var olduğu, %35,0'ında (n=123) hipertansiyon hastalığına bağlı komplikasyon geliştiği görülmüştür.

Hastaların YTD sorularına verdiği cevaplar değerlendirildiğinde; %63,2'sinin (n=222) "Hipertansiyon tanısı aldıktan sonra günlük aldığınız tuz miktarında değişiklik oldu mu?" sorusuna azalma oldu, %21,4'ünün (n=75) "Hipertansiyon tanısı aldıktan sonra kilonuzda değişim oldu mu?" sorusuna azalma oldu, %15,7'sinin (n=55) "Hipertansiyon tanısı aldıktan sonra fiziksel aktivitenizde değişiklik oldu mu?" sorusuna artış oldu, %50,7'sinin (n=178) "Hipertansiyon tanısı aldıktan sonra yemek alışkanlığınızda değişiklik oldu mu?" soruna olumlu yönde oldu şeklinde cevap verdiği görülmüştür. "Stresli bir yaşamdan kaçınmak için özen gösterir misiniz?" %54,4'ünün (n=191) bazen şeklinde cevap verdiği görülmüştür. "Eğer sigara kullanıyorsanız hipertansiyon tanısı aldıktan sonra sigara kullanma alışkanlığınızda nasıl bir değişiklik oldu?" sorusuna hastaların %25,6'sının (n=30) sigara kullanmayı bıraktım, %50,4'ünün (n=59) değişmedi cevabını verdiği görülmüştür. "Eğer alkol kullanıyorsanız hipertansiyon tanısı aldıktan sonra alkol kullanma alışkanlığınızda nasıl bir değişiklik oldu?" sorusuna hastaların %35,9'unun (n=14) alkol kullanmayı bıraktım, %38,5'inin (n=15) değişmedi cevabını verdiği tespit edilmiştir (Tablo 1).

Hastalara sorulan "Hipertansiyon tanısı aldıktan sonra günlük aldığınız tuz miktarında değişiklik oldu mu?" sorusuna YTD önerileri hakkında bilgilendirilen hastaların %67,2'si (n=201) azalma oldu, bilgilendirilmeyen hastaların %40,4'ü (n=21) azalma oldu cevabını verdiği tespit edilmiş ve azalma oldu cevabını bilgilendirilen hastaların, değişmedi cevabını bilgilendirilmeyen hastaların istatistiksel açıdan anlamlı ölçüde daha fazla verdiği görülmüştür (p=0,003). "Hipertansiyon tanısı aldıktan sonra kilonuzda değişim oldu mu?" sorusuna YTD önerileri hakkında bilgilendirilen hastaların %54,5'i (n=163) değişmedi, bilgilendirilmeyenlerde %80,8'i (n=42) değişmedi cevabını verdiği saptanmıştır. Artış oldu cevabını bilgilendirilen hastaların, azalma oldu cevabını bilgilendirilen hastaların, değişmedi cevabını bilgilendirilmeyen hastaların istatistiksel yönden anlamlı olduğu görüldü (p=0,002). "Hipertansiyon tanısı aldıktan sonra fiziksel aktivitenizde değişiklik oldu mu?" sorusuna YTD önerileri hakkında bilgilendirilen hastaların %75,9'u (n=227) değişmedi, bilgilendirilmeyen hastaların %92,3'ü (n=48) değişmedi cevabını verdiği görülmüştür. Artış oldu cevabını bilgilendirilen hastaların, değişmedi cevabını bilgilendirilmeyen hastaların

istatistiksel açıdan anlamlı ölçüde daha fazla verdiği tespit edilmiştir (p=0,012). "Hipertansiyon tanısı aldıktan sonra yemek alışkanlığınızda değişiklik oldu mu?" sorusuna YTD önerileri hakkında bilgilendirilen hastaların %56,9'u (n=170) olumlu yönde oldu, bilgilendirilmeyen hastaların %84,6'sı (n=44) değişmedi cevabını verdiği görülmüştür. Olumlu yönde oldu diyenler bilgilendirilen hastalarda, değişmedi diyenler bilgilendirilmeyen hastalarda istatistiksel açıdan anlamlı ölçüde yüksek saptanmıştır (p=0,000). Diğer YTD soruları ile YTD önerileri hakkında doktoru tarafından bilgilendirilme durumu arasında ilişki saptanmamıştır (Tablo 2).

Tablo 1.

Hastaların yaşam tarzı değişikliği sorularına verdiği cevaplar

		n	%
Hipertansiyon tanısı aldıktan sonra günlük aldığınız tuz miktarında değişiklik oldu mu?	Artış oldu	1	0,3
	Azalma oldu	222	63,2
	Değişmedi	121	34,5
	Bilinmiyor	7	2,0
Hipertansiyon tanısı aldıktan sonra kilonuzda değişim oldu mu?	Artış oldu	71	20,2
	Azalma oldu	75	21,4
	Değişmedi	205	58,4
Hipertansiyon tanısı aldıktan sonra fiziksel aktivitenizde değişiklik oldu mu?	Artış oldu	55	15,7
	Azalma oldu	21	6,0
	Değişmedi	275	78,3
Hipertansiyon tanısı aldıktan sonra yemek alışkanlığınızda değişiklik oldu mu?	Olumlu yönde oldu	178	50,7
	Olumsuz yönde oldu	4	1,1
	Değişmedi	169	48,2
Stresli bir yaşamdan kaçınmak için özen gösterir misiniz?	Her zaman	29	8,3
	Sık sık	64	18,2
	Bazen	191	54,4
	Hiçbir zaman	67	19,1
Eğer sigara kullanıyorsanız hipertansiyon tanısı aldıktan sonra sigara kullanma alışkanlığınızda nasıl bir değişiklik oldu?	Sigara kullanmayı bıraktım	30	25,6
	Sigara miktarını azalttım	27	23,1
	Sigara miktarını arttırdım	1	0,9
	Sigara kullanmaya başladım	0	0
	Değişmedi	59	50,4
Eğer alkol kullanıyorsanız hipertansiyon tanısı aldıktan sonra alkol kullanma alışkanlığınızda nasıl bir değişiklik oldu?	Alkol kullanmayı bıraktım	14	35,9
	Alkol miktarını azalttım	10	25,6
	Alkol miktarını arttırdım	0	0
	Alkol kullanmaya başladım	0	0
	Değişmedi	15	38,5

Tablo 2.

Bilgilendirilme durumlarına göre hastaların yaşam tarzı değişikliği sorularına verdiği cevaplar

		Doktorunuz tarafından yaşam tarzı değişiklik önerileri hakkında bilgilendirildiniz mi?				p
		Evet		Hayır		
		n	%	n	%	
Hipertansiyon tanısı aldıktan sonra günlük aldığınız tuz miktarında değişiklik oldu mu?	Artış oldu	1	0,3	0	0	**0,003***
	Azalma oldu	201	67,2	21	40,4	
	Değişmedi	92	30,8	29	55,8	
	Bilinmiyor	5	1,7	2	3,8	
Hipertansiyon tanısı aldıktan sonra kilonuzda değişim oldu mu?	Artış oldu	65	21,7	6	11,5	**0,002***
	Azalma oldu	71	23,7	4	7,7	
	Değişmedi	163	54,5	42	80,8	
Hipertansiyon tanısı aldıktan sonra fiziksel aktivitenizde değişiklik oldu mu?	Artış oldu	54	18,1	1	1,9	**0,012***
	Azalma oldu	18	6,0	3	5,8	
	Değişmedi	227	75,9	48	92,3	
Eğer sigara kullanıyorsanız hipertansiyon tanısı aldıktan sonra sigara kullanma alışkanlığınızda nasıl bir değişiklik oldu?	Sigara kullanmayı bıraktım	24	25,3	6	27,3	0,967
	Sigara miktarını azalttım	22	23,2	5	22,7	
	Sigara miktarını arttırdım	1	1,1	0	0	
	Sigara kullanmaya başladım	0	0	0	0	
	Değişmedi	48	50,5	11	50,0	
Eğer alkol kullanıyorsanız hipertansiyon tanısı aldıktan sonra alkol kullanma alışkanlığınızda nasıl bir değişiklik oldu?	Alkol kullanmayı bıraktım	13	40,6	1	14,3	0,384
	Alkol miktarını azalttım	8	25,0	2	28,6	
	Alkol miktarını arttırdım	0	0	0	0	
	Alkol kullanmaya başladım	0	0	0	0	
	Değişmedi	11	34,4	4	57,1	
Hipertansiyon tanısı aldıktan sonra yemek alışkanlığınızda değişiklik oldu mu?	Olumlu yönde oldu	170	56,9	8	15,4	**0,000***
	Olumsuz yönde oldu	4	1,3	0	0	
	Değişmedi	125	41,8	44	84,6	
Stresli bir yaşamdan kaçınmak için özen gösterir misiniz?	Her zaman	21	7,0	8	15,4	**0,154**
	Sık sık	58	19,4	6	11,5	
	Bazen	163	54,5	28	53,8	
	Hiçbir zaman	57	19,1	10	19,2	

Ki kare testi, *: p<0,05

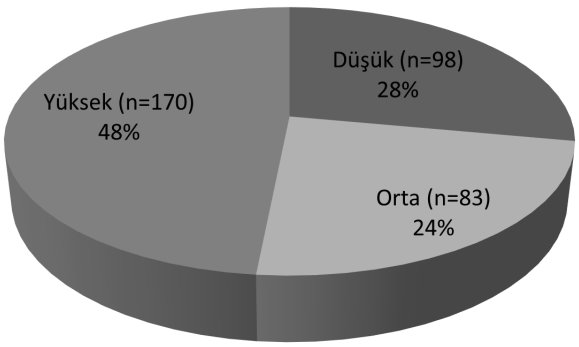
Morisky tedavi uyumu ölçeğine göre tedavi uyumunun dağılımı değerlendirildiğinde hastaların %28,0'ının (n=98) tedavi uyumu düşük, %24,0'ının (n=83) orta, %48,0'ının (n=170) yüksek tespit edilmiştir (Şekil 1).

Tedavi uyumu tansiyonlarını düzenli ölçenlerin %51,1'inde (n=45), bazen ölçenlerin %52,0'ında (n=92), düzenli ölçmeyenlerin %38,4'ünde (n=33) yüksek bulunmuş ve düzenli ve bazen ölçenlerde düzenli ölçmeyenlere göre tedavi uyumu yüksek olanların oranı istatistiksel olarak anlamlı düzeyde yüksek bulunmuştur (p=0,001) (Tablo 3).

Tablo 4'te hastaların YTD sorularına verdiği cevaplar ile Morisky tedavi uyumu arasındaki ilişki değerlendirilmiştir. "Günlük tuz alımınız 5-6 gramdan (1 çay kaşığı) fazla mıdır?" sorusuna evet cevabı veren hastaların %40,8'inde (n=60), hayır cevabı veren hastaların %53,9'unda (n=110) tedavi uyumu yüksek bulunmuş ve hayır cevabı verenlerde tedavi uyumu istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır. Diğer YTD soruları ile Morisky tedavi uyumu arasında istatistiksel olarak anlamlı düzeyde ilişki saptanmamıştır (Tablo 4).

Şekil 1.

Morisky tedavi uyumu ölçeğine göre tedavi uyumunun dağılımı



Tablo 3.

Hastaların tansiyon ölçme özelliklerine göre Morisky tedavi uyumunun değerlendirilmesi

		Morisky Tedavi Uyumu						p
		Düşük		Orta		Yüksek		
		n	%	n	%	n	%	
Evde tansiyon ölçüm aletiniz var mı?	Var	76	25,0	73	24,0	155	51,0	**0,006***
	Yok	22	46,8	10	21,3	15	31,9	
Tansiyonlarınızı düzenli ölçer misiniz?	Evet	15	17,0	28	31,8	45	51,1	**0,001***
	Bazen	45	25,4	40	22,6	92	52,0	
	Hayır	38	44,2	15	17,4	33	38,4	

Ki kare testi,

Tablo 4.

Hastaların yaşam tarzı değişikliği sorularına verdiği cevaplar ile Morisky tedavi uyumu arasındaki ilişkinin değerlendirilmesi

		Morisky Tedavi Uyumu						p
		Düşük		Orta		Yüksek		
		n	%	n	%	n	%	
Günlük tuz alımınız 5-6 gramdan (1 çay kaşığı) fazla mıdır?	Evet	49	33,3	38	25,9	60	40,8	**0,045***
	Hayır	49	24,0	45	22,1	110	53,9	
Hipertansiyon tanısı aldıktan sonra günlük aldığınız tuz miktarında değişiklik oldu mu?	Artış oldu	0	,0	0	,0	1	100,0	0,253
	Azalma oldu	57	25,7	47	21,2	118	53,2	
	Değişmedi	38	31,4	35	28,9	48	39,7	
	Bilinmiyor	3	42,9	1	14,3	3	42,9	
Hipertansiyon tanısı aldıktan sonra kilonuzda değişim oldu mu?	Artış oldu	24	33,8	19	26,8	28	39,4	0,505
	Azalma oldu	19	25,3	19	25,3	37	49,3	
	Değişmedi	55	26,8	45	22,0	105	51,2	
Hipertansiyon tanısı aldıktan sonra fiziksel aktivitenizde değişiklik oldu mu?	Artış oldu	17	30,9	11	20,0	27	49,1	0,611
	Azalma oldu	7	33,3	7	33,3	7	33,3	
	Değişmedi	74	26,9	65	23,6	136	49,5	
Hipertansiyon tanısı aldıktan sonra yemek alışkanlığınızda değişiklik oldu mu?	Olumlu yönde oldu	42	23,6	42	23,6	94	52,8	0,257
	Olumsuz yönde oldu	2	50,0	0	,0	2	50,0	
	Değişmedi	54	32,0	41	24,3	74	43,8	
Stresli bir yaşamdan kaçınmak için özen gösterir misiniz?	Her zaman	8	27,6	9	31,0	12	41,4	0,811
	Sık sık	15	23,4	14	21,9	35	54,7	
	Bazen	54	28,3	47	24,6	90	47,1	
	Hiçbir zaman	21	31,3	13	19,4	33	49,3	

Ki kare testi

Yaşadığı bölgeye göre yapılan karşılaştırmada; kırsal bölgede yaşayanların kentsel bölgede yaşayanla göre tedavi uyumu istatistiksel olarak anlamlı düzeyde yüksek (p 0,009) tespit edilmiştir. Kontrollere düzenli olarak giden hastalarda tedavi uyumu, kontrollere düzenli olarak gitmeyen hastalarda göre istatistiksel olarak anlamlı düzeyde yüksek bulunmuştur (p=0,005).

4. TARTIŞMA

Çalışmamızda hipertansiyon hastalarının yaklaşık %20'sinin (n=70) önerilen kanıta dayalı YTD'den hiçbirini uygulamadığı, sadece üç hastanın ise bu değişikliklere tamamen uyum sağladığı belirlenmiştir. Katılımcıların %85,2'sinin çoğunun YTD konusunda bilgilendirildiği görülmüştür. Bu hastaların, tuz kısıtlaması, kilo kontrolü, fiziksel aktivite ve diyet önerilerine, bilgilendirilmeyen hastalara kıyasla anlamlı derecede daha yüksek uyum gösterdikleri tespit edilmiştir. Katılımcıların ilaç tedavilerine uyum oranlarının, YTD'ye uyum oranlarından daha yüksek olduğu gözlemlenmiştir. Hastaların yaklaşık yarısının ilaç tedavilerine "yüksek uyum", %27,92'sinin ise "düşük uyum" gösterdiği saptanmıştır.

Çalışmamızda, hipertansiyon hastalarına önerilen kanıta dayalı YTD'ye katılımcıların uyum düzeyleri değerlendirildiğinde, büyük bir kısmının bu önerilere yeterince uyum göstermediği, ancak ilaç tedavisine uyumlarının YTD'ye göre daha iyi olduğu tespit edilmiştir. Ayrıca, ilaç tedavisine uyum ile yaşam tarzı önerilerine uyum arasında pozitif yönde anlamlı bir ilişki bulunmuştur. Bunun yanında, erkeklerin kadınlara, gençlerin yaşlılara, ve eğitim düzeyi yüksek olanların düşük eğitim düzeyindekilere kıyasla YTD'ye daha fazla uyum sağladığı belirlenmiştir. Buna karşın, kadınların erkeklere, yaşlıların gençlere, ve düşük eğitim düzeyine sahip olanların yüksek eğitim düzeyindekilere göre ilaç tedavisine daha fazla uyum gösterdiği, ancak bu farkın istatistiksel olarak anlamlı olmadığı gözlemlenmiştir. Hem YTD'ye hem de ilaç tedavisine uyumun, evli bireylerde bekarlara göre daha yüksek olduğu görülmüştür

Yaşam tarzı değişiklikleri hakkında bilgilendirilen katılımcıların, bilgilendirilmemiş hastalara kıyasla günlük tuz tüketimlerini daha fazla azalttıkları tespit edilmiştir. Sacks ve arkadaşlarının ABD'de 412 hasta ile gerçekleştirdikleri bir çalışmada, tuz tüketiminin azaltılmasının kan basıncında 4,6 mm Hg'ye kadar düşüşlere yol açtığı belirlenmiştir.[9] Kanada'da 23,129 kişinin katıldığı bir çalışmada, diyetteki tuz miktarı azaltılmasının bir yılda görülen 11.550 kardiyovasküler olayı önleyeceği tahmin edilmektedir. Bu yolla, doktor ve laboratuvar harcamalarında %6,5, hipertansiyon tanısı olan hastaların ilaç ihtiyaçlarında %23 azalma olacağı bildirilmiştir.[10] Hipertansiyon tanılı hastaların her muayenesinde tuz kısıtlanması yönünde önerilerde bulunulmasının öneminin unutulmaması gerektiğini düşünmekteyiz.

Bulgularımızda yaşam tarzı değişiklikleri konusunda bilgilendirilen hastaların, bilgilendirilmemiş hastalara kıyasla hipertansiyon tanısı aldıktan sonra kilo kaybı yaşadıkları belirlenmiştir. Çakır'ın 2003 yılında gerçekleştirdiği bir çalışmada ise, hipertansif bireylere sağlıklı yaşam tarzı davranışlarını teşvik eden eğitimlerin verilmesi sonrası deney grubunda kilo, bel çevresi ve beden kitle indeksinde anlamlı bir azalma gözlemlenmiş ve bu durumun kan basınçlarını önemli ölçüde düşürdüğü, kontrol grubunda ise benzer bir düşüşün olmadığı tespit edilmiştir.[11] Çakır'ın çalışmasının da bulgularımızla uyumlu olduğu görülmektedir. Hipertansif bireylerde kilo takibinin yapılması ve fazla kiloların verilmesi için ilgili birimlere yönlendirmenin, tedaviyi destekleyici önemli bir unsur olduğunu düşünmekteyiz.

Çalışmamızda, YTD konusunda bilgilendirilen hastaların, bilgilendirilmeyen hastalara kıyasla hipertansiyon tanısı sonrasında fiziksel aktivitelerinde artış gösterdikleri belirlenmiştir. Kim ve Kong'un 2015 yılında Güney Kore'de 3802 hasta ile gerçekleştirdikleri bir çalışmada, hipertansif hastaların önerilen fiziksel aktivitelere %46 oranında uyum sağladıkları tespit edilmiştir.[12] Kanada'da 1281 hastayla yürütülen bir çalışmada, hastalara YTD eğitimi verildikten sonra sadece %7,9'unun fiziksel aktivitelerinde iyileşme sağlandığı bulunmuştur.[13] Ülkemizde yapılan bir çalışmada, katılımcıların egzersiz alışkanlıkları incelenmiş ve elde edilen verilere göre, katılımcıların %55,3'ünün hiç egzersiz yapmadığı, %26,7'sinin ise haftada 3 gün ve üzeri, minimum 30 dakika süreyle egzersiz yaptığı saptanmıştır.[14] Hipertansiyon hastalarının her kontrol muayenelerinde fiziksel aktivitelerini arttırmalarını, hareketsiz yaşamdan kaçınmalarını tavsiye etmenin yararlı olacağını düşünmekteyiz.

Çalışmamızda, YTD konusunda bilgilendirilen hastaların, bilgilendirilmeyenlere kıyasla hipertansiyon tanısı sonrasında beslenme alışkanlıklarını olumlu yönde değiştirdikleri tespit edilmiştir. Amerika'da 810 hasta üzerinde gerçekleştirilen bir çalışmada, DASH diyeti eğitimi verilen hastaların %66'sının bu diyeti uyguladığı, uygulayanların %77'sinde ise kan basıncında önemli düşüşler kaydedildiği gösterilmiştir.[15] Kurçer ve Özbay, koroner arter hastalarını dahil ettiği çalışmada verilen eğitim sonrasında hastaların beslenme alışkanlıklarıyla alakalı bilgi düzeylerinin artışına paralel olarak diyete uyumlarının arttığı, kan basıncı düzeylerinde anlamlı ölçüde azalma olduğunu göstermiştir.[16] Bu çalışmalar, çalışmamızı desteklemekte olup, hipertansif hastalara beslenme konusunda bilgi vermenin, her muayenede hatırlatmanın, gerekirse ilgili birimlere yönlendirmenin faydalı olacağı kanaatindeyiz.

Hastaların yarısından azında ilaç tedavisine yüksek uyumu saptadık. Irmak ve ark. sınırlı bir grup hastada yaptıkları müdahale çalışmasında katılımcıların neredeyse tamamının ilaç tedavisine tam uyum gösterdiği saptanmıştır.[17] Atik ve ark. Hipertansif hastaların ilaç tedavisine uyumlarının değerlendirildiği araştırmada; ilaç tedavilerine uyumun %60 civarında olduğu belirtilmiştir.[18] Gökçeimam ve ark. hipertansiyon hastalarının bilinçli farkındalık düzeyleri ile ilaç tedavisine uyumları arasındaki ilişkisini değerlendirdiği bir başka çalışmada ise uyum oranlarının düşük seviyelerde olduğunu saptamıştır.[19] Alhaddad ve ark. yaptıkları çalışmada, tedaviye uyumlu hastaların oranının %55,9 olduğunu tespit etmiştir. Ayrıca, tedaviye uyumun standardize bir yöntemle değerlendirilememesinin farklı sonuçlara neden olabileceği de öne sürülmüştür.[20] Literatürde, hipertansiyon hastalarının ilaç tedavisine uyumlarının değerlendirildiği çeşitli popülasyonlarda yapılmış birçok çalışma bulunmakta ve bu çalışmaların sonuçları arasında farklılıklar gözlemlenmektedir. Çalışmamızda, ilaç tedavisine yüksek uyum oranının %48 olduğu saptanmıştır. Bu literatür farklılıklarının araştırma yapılan popülasyona bağlı olarak değişebileceği düşünülmektedir. Bu değişkenliğin daha iyi anlaşılabilmesi için daha kapsamlı araştırmaların yapılması gerektiği kanaatindeyiz.

Kronik hastalıkların yönetiminde olduğu gibi, hipertansiyon tedavisinde de medikal tedavi kadar YTD de büyük önem taşımaktadır. Hipertansiyonun tedavi planının ilk aşaması, YTD'yi içermektedir. Özellikle düşük riskli hastalar için yaşam tarzı müdahalesi, tek başına etkili bir tedavi seçeneği olabilmektedir. Çalışmamızda, YTD'yi uygulayan hastaların ilaç tedavisine uyumlarının daha yüksek olduğu gözlemlenmiş olmasına rağmen, bu tür müdahaleleri uygulayan hasta sayısının oldukça düşük olduğu belirlenmiştir. Doktorların

ilaç tedavilerini düzenlemeleri rağmen, hastaların tedaviye uyum göstermemesi kan basıncının kontrolünü zorlaştırmaktadır. Hastaların YTD'yi anlamaları ve uygulamaları konusunda desteklenmeleri ile düzenli doktor kontrollerine gitmeleri, hem YTD'ye hem de ilaç tedavilerine uyumlarını artırabilir.

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Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

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Research Article

Evaluation of Antiplatelet/Anticoagulant Use and Prognosis in Primary Thrombophilia Patients with COVID-19

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Objective: This study is aimed to investigate the relationship between inherited thrombophilia and COVID-19 symptoms and the outcomes of treatment strategies.

Materials and Methods: This descriptive and retrospective study included patients who were followed up for thrombophilia in a training and research hospital. Data from 121 patients who had COVID-19 infection and those who met the inclusion criteria were collected through retrospective examination of medical records and telephone interviews using a data collection form developed by the researchers. The data obtained from the study was evaluated using descriptive and comparative statistical methods.

Results: Among the patients diagnosed with COVID-19, 11.6% had severe clinical presentations requiring intensive care support. During COVID-19 infection, mostly no drug was preferred for treatment (51.2%), and the most preferred drug was acetylsalicylic acid (ASA) (33.1%). A total of 13 thromboembolic events occurred in 12 patients who were included in the study during and after COVID-19 infection. No thromboembolic events occurred in patients using warfarin or new-generation oral anticoagulants during COVID-19. There was no significant difference in thromboembolism complications among patients who did not use any medication, those who used ASA/clopidogrel, and those who used low molecular weight heparin during COVID-19 infection. The most common gene mutation in the study was plasminogen activator inhibitor-1 (PAI-1) mutation, and there was no statistically significant difference between PAI-1 gene mutation and new thrombotic events (p=0.988).

Conclusion: COVID-19 infection was found to cause bilateral lung involvement with diffuse microthrombi in patients with genetic thrombophilia. No new thromboembolic events occurred in patients with thrombophilia using warfarin or new-generation oral anticoagulants.

Keywords: Coronavirus, Hereditary thrombophilia, Coagulation, Anticoagulation, Thrombosis

1. INTRODUCTION

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are more likely to develop venous, cerebrovascular, and coronary thrombi, especially if they have severe coronavirus illness (COVID-19). Although further research is needed, the pathophysiology is complicated and likely involves proinflammatory cascades, coagulopathy, and neutrophil extracellular traps (1). The dysregulated connection between innate immunity and coagulation is sometimes called immuno-thrombosis (2, 3). Through the angiotensin-converting enzyme 2 (ACE2) receptor, the SARS-CoV-2 virus directly infects endothelial cells. This causes viral inclusion bodies to form in the lungs, liver, small intestines, and kidneys, as well as the loss of endothelial glycocalyx proteins and a drop in heparanase-2 levels. As a result, the patient progresses from normal hemostasis to an antifibrinolytic state (4).

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Inherited thrombophilia diaseas are rare diseases characterized by prolonged bleeding time resulting from deficiencies in protein cofactors and enzymes that play a role in blood clotting.

Classical inherited thrombophilia includes loss-of-function variants in the genes that encode the natural anticoagulant proteins, antithrombin (AT), protein C (PC), and protein S (PS), and gain-of-function mutations in the genes encoding factor V (factor V Leiden (FVL)) and prothrombin (FII) (previous nomenclature G20210A). Rarer congenital thrombophilias have been described in the literature, such as genetically determined increased homocysteine levels, coagulation factors (VIII and IX), and hypodysfibrinogenemia. Venous thromboembolic disease (VTD) is a multifactorial disease resulting from the interaction between environmental, clinical, and biological risk factors (5,6). Each thrombophilic abnormality significantly increases the risk of thrombosis, especially if combined with additional factors such as COVID-19 (7). For prevention, several antithrombotic medicines have been proposed as potential therapy for COVID-19-associated thrombosis. Many of these drugs also have pleiotropic anti-inflammatory or antiviral effects. The growing awareness and mechanistic understanding of COVID-19 patients' prothrombotic state drives efforts toward more stringent diagnostic screening for thrombotic complications and the early administration of antithrombotic drugs to prevent and treat thrombotic complications (8). This study is aimed to investigate the association between inherited thrombophilias and COVID-19 manifestations and outcomes of treatment strategies.

2. MATERIALS AND METHODS

Before starting the study approval was obtained from the local ethics committee (E-71522473-050.01.04-651) and the Scientific Research Platform of the Ministry of Health of the Republic of Türkiye (2020-10-21T15_38_25). Two thousand seventy-nine patients who were diagnosed with thrombophilia between the dates of June 2017 and October 2020 were analyzed retrospectively referring to Sakarya University Training and Research Hospital Genetic Diseases Research Outpatient Clinic. Among the evaluated patients, 1856 patients who did not have COVID-19 during the COVID-19 pandemic were excluded from the study. Inclusion criteria for the study were patients who were between the age of 18 and 90, and those who had applied to the genetic diseases research outpatient clinic due to any thrombotic event, and the ones who had a coronavirus infection during the COVID-19 pandemic. Patients with no gene mutation predisposing to thrombosis during gene screening or who did not have a COVID-19 history and were pregnant, and breastfeeding were excluded from the study. Two hundred twelve patients who met the current criteria were called to inquire whether they used anticoagulant treatment before, during, and after the COVID-19 treatment. Ninety patients who could not be reached by phone or who refused to participate in the study were excluded from the study, and 121 patients, who were evaluated by age, gender, disease severity, gene mutation causing thrombosis, use of anticoagulants, use of antiaggregants, a new thrombotic event during and after COVID-19 infection were recorded by questioning.

2.1. Statistical analysis

Data analysis was performed using SPSS-22 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z). The variables were investigated using visual (histograms, probability plot) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are typically distributed. Frequency tables interpret categorical variables. The continuous variables were expressed as

mean and standard deviation. Categorical features and relationships between groups were assessed using an appropriate chi-square test. The statistically significant two-tailed p-value was considered as <0.05.

3. RESULTS

The study included 121 COVID-19 patients who had previously performed gene mutation analysis for thrombophilia in the hospital and had positive results in any parameter. Twenty patients (16.5%) were male. Patients in the study group had a mean age of 39.3±10.2. The clinical course of patients 14 (11.6%) were severe and required intensive care support. The mutation analysis results of MTHFR C677T, PAI, MTHFR A1298C, Factor 5 Leiden, Factor 13, and Factor 2 are summarized in Table 1

Table 1.

Baseline clinical characteristics of the patients

	Results (n=121)
Age	39.3±10.2
Gender, male, n (%)	20 (16.5)
Disease severity, n (%) *Critical patients* *Non-critical patients*	 14 (11.6) 107 (88.4)
MTHFR C677T mutation *Homozygous* *Heterozygous* *Absent*	 6 (5) 53 (43.8) 62 (51.2)
Plasminogen activator inhibitör-1 mutation *Homozygous* *Heterozygous* *Absent*	 31 (25.6) 58 (47.9) 32 (26.4)
MTHFR A1298C mutation *Homozygous* *Heterozygous* *Absent*	 15 (12.4) 54 (44.6) 52 (43.0)
Factor 5 Leiden mutation *Homozygous* *Heterozygous* *Absent*	 1 (0.8) 10 (8.3) 110 (90.9)
Factor 13 mutation *Homozygous* *Heterozygous* *Absent*	 4 (3.3) 32 (26.4) 85 (70.2)
Factor 2 mutation *Homozygous* *Heterozygous* *Absent*	 - 5 (4.1) 116 (95.9)

Peripheral arterial disease (38.0%) was the most common accompanying chronic complication, and abortus was the most common thrombotic event (54.5%). Before the COVID-19 infection, prophylaxis of coagulation was mostly not preferred (57.0%), and the most frequently preferred drug for prophylaxis was acetylsalicylic acid (ASA)/clopidogrel (28.9%). Also, during COVID-19 infection, no drug was preferred for treatment (51.2%), and the most preferred drug was ASA/clopidogrel (33.1%) (Table 2).

During and after the COVID-19 infection of the patients included in the study, six patients had minor ischemic stroke (AMIS), three had new abortion, two had cerebrovascular accident (CVA), one had pulmonary thromboembolism, and one had acute critical leg ischemia; a total of 13 thromboembolic events developed in 12 patients.

Among the patients with a positive thrombophilia panel, patients with and without a new thromboembolic event during COVID-19 infection were compared in terms of pulmonary involvement, and bilateral pulmonary involvement was significantly higher in the group with the event (66.7% vs 28.4% respectively, p=0.007) (Figure 1).

Table 2.

Chronic complications and antiaggregant/anticoagulant drugs of choice before and during COVID-19

	Results (n=121)
Chronic diseases, yes (%)	
Diabetes mellitus	11 (9.1)
Hypertension	16 (13.2)
COPD	10 (8.3)
ASCVD	7 (5.8)
Chronic renal failure	1 (0.8)
Peripheral arterial disease	46 (38.0)
Cerebrovascular disease	15 (12.4)
History of abortus	66 (54.5)
History of pulmonary thromboembolism	7 (5.8)
History of deep vein thrombosis	3 (2.5)
Anticoagulant/antiaggregant drugs of choice before COVID-19, n (%)	
ASA/Clopidogrel	35 (28.9)
Warfarin	4 (3.3)
Low molecular weight heparin	9 (7.4)
Novel Oral Anticoagulants	4 (3.3)
Absent	69 (57.0)
Anticoagulant/antiaggregant drugs of choice during COVID-19, n (%)	
ASA/Clopidogrel	40 (33.1)
Warfarin	4 (3.3)
Low molecular weight heparin	11 (9.1)
Novel Oral Anticoagulants	4 (3.3)
Absent	62 (51.2)

The frequency of newly developing thromboembolic events was compared according to the thrombophilia gene mutation, and no significant difference was found in any of the subgroups (Table 3).

No new thromboembolic events occurred in patients using warfarin (n=4) and new-generation oral anticoagulants (n=4) during Covid-19 infection. Complications of thromboembolism developed in 4 (6.5%) patients who did not use any drugs (n=62), 6 (15.0%) patients who used ASA/ Clopidogrel (n=40), and 2 (18.2%) patients who used low molecular weight heparin (n=11) and no significant difference was observed between the groups (Figure 2).

Figure 1.

Comparison of bilateral pulmonary involvement of COVID-19 in cases with new thrombotic events

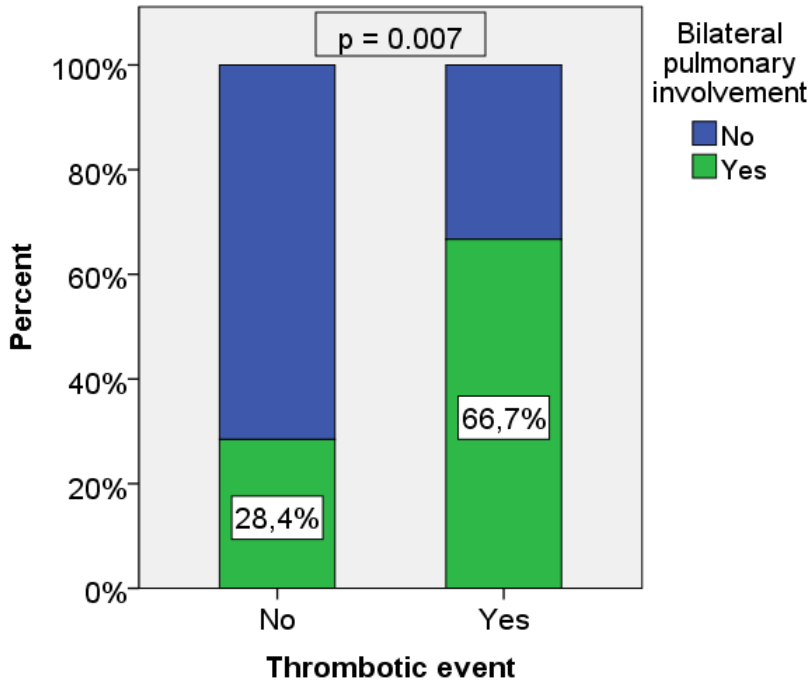


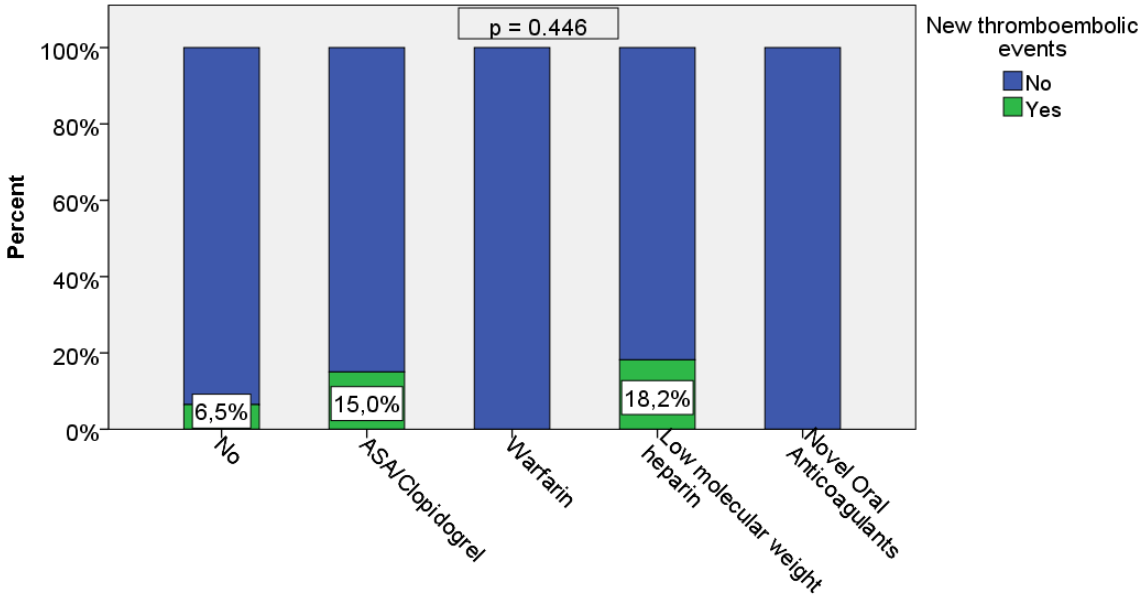
Table 1.

Comparison of new thromboembolic events according to thrombophilia gene mutation

	Homozygous	Heterozygous	Absent	P value
MTHFR C677T, n (%)	2 (33.3)	3 (5.7)	7 (11.3)	0.087
Plasminogen activator inhibitor-1, n (%)	3 (9.7)	6 (10.3)	3 (9.4)	0.988
MTHFR A1298C, n (%)	2 (13.3)	6 (11.1)	4 (7.7)	0.752
Factor 5 Leiden, n (%)	-	-	12 (10.9)	0.514
Factor 13, n (%)	-	3 (9.4)	9 (10.6)	0.781
Factor 2, n (%)	-	1 (20.0)	11 (9.5)	0.441

Figure 2.

Comparison of the frequency of new thromboembolic events by drug of choice



4. DISCUSSION

Many factors affect the development of thrombosis. Genetic diseases predisposing to thrombosis may trigger diseases with pathological thrombotic processes, such as COVID-19. This study's most common gene mutation was plasminogen activator inhibitor-1 (PAI-1) mutation with 89 cases. However, no significant statistical difference was found in this research regarding PAI-1 gene mutation and new thrombotic events (p = 0.988). When the frequency of newly developed thrombotic events was compared in patients with COVID-19, whose gene analyses were positive in the hospital with suspected genetic disease causing thrombosis, tall subgroups had no statistically significant difference. Still, a partially significant outcome was revealed in patients with MTHFR C677T gene mutation (p = 0.087). MTHFR C677T I is a gene mutation that causes high blood homocysteine levels. Homocysteine is a molecule that causes ischemic heart disease, peripheral arterial disease, ischemic stroke, and venous thrombosis. It achieves this effect by upregulating the angiotensin receptor and renin-angiotensin-aldosterone system components (9,10). Homocysteine has also been shown to play a role in the mechanism of action of SARS-CoV-2 infection by causing angiotensin II receptor activation (11-13). Therefore, although a partially significant difference was found, it may be said that genetic mutations associated with hyperhomocysteinemia are the most effective thrombophilias that stimulate the emergence of thrombotic complications of COVID-19 infection. More studies with higher sample sizes are needed to assess the effect of hyperhomocysteinemia during COVID-19 infection. Fox et al, (14) revealed diffuse microthrombi were detected in the pulmonary autopsies of COVID-19 patients with pulmonary involvement. In this study, the results of patients with gene mutations predisposing to thrombosis in genetic screening were presented, and patients with and without a new thromboembolic event during COVID-19 infection were compared regarding lung involvement. Bilateral lung involvement was significantly higher in the group with thromboembolic events (p = 0.007).

One study has been published investigating the possible correlation of thrombotic events with hereditary thrombophilia factors in patients who died of COVID-19 (15). The authors evaluated the mutations in FV 506R/Q, MTHFR 223A/V, F2 20210G/A and PAI-1 4G/5G. The results obtained by them show that the highest percentage was detected in pulmonary artery thrombosis, followed by pulmonary embolism. Additionally, the incidence of MTHFR 223A/V

heterozygous and PAI-1 4G/5G heterozygous genotypes was higher in patients with COVID-19 and thrombotic events, and that of FV 506R/Q and F2 20210G/A heterozygotes was lower. (15). The MTHFR gene encodes 5,10-methylenetetrahydrofolate reductase, which is involved in homocysteine metabolism. The severity of COVID-19 could be associated with HHcy and possibly with depleted folic acid in infected cells (16-19). HHcy was correlated with an increase in the incidence and severity of COVID-19 (20). In this study, while MTHFR and PAI were high, FV was low.

Low molecular weight heparin is the most commonly used anticoagulant to avoid thrombotic complications during severe COVID-19 infection (21). In this study, while the majority of patients (51.2%) did not use drugs, ASA/clopidogrel (33.1%) was the most preferred among drug users. The clinical severity of the disease differs in the cases since the patient group included in this study was a patient population with mutations detected in gene screening and who had COVID-19 infection. Previous research on the preventive role of chronic oral anticoagulation in COVID-19 hospitalized patients yielded conflicting results (22-28). Russo et al. 0) revealed no significant association among oral anticoagulants, neither with Novel Oral Anticoagulants (NOACs) nor vitamin K antagonists, and the severity of the disease regarding ARDS in hospitalized patients due to COVID-19 infection (22). As potential therapies for preventing thrombosis associated with COVID-19, antithrombotic drugs, including heparin, factor XII inhibitors, and fibrinolytic drugs, have been administered (29,30). One guide to thromboprophylaxis in COVID-19 recommends routine doses of thromboprophylaxis in the absence of contraindications in the hospital, increased intensity thromboprophylaxis in the intensive care unit, and consideration of anticoagulant thromboprophylaxis in patients with increased risk of venous thromboembolism post-hospital (31). In this study, although not statistically significant, no new thromboembolic event has developed in any of the patients using warfarin and new-generation oral anticoagulants. Very few publications have reported the results of patients with COVID-19 infection who have a genetic tendency to thrombosis. This study is one of the rare studies investigating the severity of the disease, the use of anticoagulants, and the effect of gene mutations on the disease in this group of patients. This study is limited by the retrospective design and the relatively small sample size of patients on anticoagulation therapy.

5. CONCLUSION

In conclusion, this study objectively evaluated the outcomes of patients with any gene mutation that causes thrombophilia who have had a COVID-19 infection retrospectively. This study also reveals that COVID-19 infection causes bilateral pulmonary involvement with diffuse microthrombi in patients with genetic thrombophilia. Especially high homocysteine levels in the blood are partially related to this thrombotic event. No new thrombotic events are developed in thrombophilia patients using warfarin and new-generation oral anticoagulants.

Congress:

The study was not presented at any scientific event.

Ethics Committee Approval:

This study was approved by the clinical research ethics committee of the Sakarya University. Date: 28.12.2020, number: 651.

Informed Consent:

Since the study had a retrospective design, consent could not be obtained from the patients.

Conflict of Interest:

None declared by the authors.

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Case Report/ Olgu Sunumu

Nadir Bir Olgu: Genişlemiş Virchow-Robin Boşluklarına Bağlı Kognitif Bozukluk

A Rare Case: Cognitive Impairment Due to Enlarged Virchow-Robin Spaces

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Giriş: Virchow-Robin boşlukları olarak bilinen perivasküler boşluklar, metabolik atıkları temizlemek için beyin omurilik sıvısı (BOS) ve interstiyel sıvının astrositik aquaporin 4 (AQP4) kanalları yoluyla değişimine izin vermektedir. Glimfatik sistemde bu perivasküler boşlukların mekanizmasında ortaya çıkan aksamalar, nörodejeneratif hastalıkların oluşum mekanizmalarından biri olarak gösterilmektedir. Bu yazımızda demansiyel süreç ile takip edilen, nörogörüntülemesinde genişlemiş Virchow-Robin boşlukları saptanan, nadir görülen bir olguyu sunmayı amaçladık.

Olgu: Seksen yaşında kadın hastanın yaklaşık altı yıl önce başlayan ve giderek artan unutkanlık şikayetleri olduğu öğrenildi. Özgeçmişinde Alzheimer tipi demans ön tanısı olduğu öğrenildi. Nörolojik muayenesinde genel durum iyi, şuuru açık, koopereydi, kişi ve zaman dezoryanteydi. Toplam 30 puanlık mini mental test 13 puan saptandı. Kranial manyetik rezonan görüntüleme (MRG) de her iki serebral hamisferde yaygın perivasküler genişleme ve T2 hiperintensiteleri ve konveksite düzeyinde mikrohemoraji odakları izlendi. Dört yıl önce de çekilen kranial MRG da perivasküler genişlemeler izlendi. Serebral amiloid anjiopati ön tanısı ile interne edildi ve 1 mg/kg dan kortikoteroid tedavisi verildi. Kortikosteroid tedavisi ile semptomları gerilemeyen olgunun kranial MRG'si nöroradyoloji konseyinde Virchow-Robin boşluklarının genişlemeleri olarak değerlendirildi.

Tartışma: Bu perivasküler boşlukların genişlemesi yüksek olasılıkla ileri yaş, hipertansiyon ve aterosklerotik karotis plakları gibi arteryel damarlardaki patolojiler ve nabızda izlenen dalgalanmalar ile açıklanmaya çalışılmıştır. Perivasküler boşluklardaki bu genişlemelerin daha çok bazal ganglionlar ve sentrum semiovalede görüldüğü bildirilmiş. Bizim olgumuzda ön planda amilod anjiopatide düşünülse de kortikosteroide tedavi yanıtı alınamamıştır. Nöroradyoloji konseyinde MRG lezyonlarının Virchow-Robin boşluklarının genişlemesi lehine değerlendirilmesi üzerine, bu perivasküler boşlukların genişlemelerinin demans riskinde artışa neden olabileceğini vurgulamak amacıyla sunuma değer görülmüştür.

Anahtar kelimeler: Virchow-Robin boşlukları, Demans, Genişleme

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Introduction: Perivascular spaces, known as Virchow-Robin spaces, allow the exchange of cerebrospinal fluid (CSF) and interstitial fluid for the clearance of metabolic waste through astrocytic aquaporin 4 (AQP4) channels. Disruptions in the mechanism of these perivascular spaces in the glymphatic system are suggested as one of the mechanisms underlying the development of neurodegenerative diseases. In this article, we aim to present a rare case followed by a dementia process with enlarged Virchow-Robin spaces detected in neuroimaging.

Case: It was learned that an eighty-year-old female patient had complaints of progressive forgetfulness that began approximately six years ago. It was found that she had a preliminary diagnosis of Alzheimer's-type dementia in her medical history. Upon neurological examination, the patient was in good general condition, conscious, cooperative, but disoriented in person and time. A total score of 13 points was determined on the Mini-Mental State Examination. Cranial magnetic resonance imaging (MRI) revealed widespread perivascular enlargement and T2 hyperintensities in both cerebral hemispheres, as well as microhemorrhagic foci at the level of convexity. Cranial MRI taken four years ago also showed perivascular enlargements. She was admitted with a diagnosis of cerebral amyloid angiopathy and was treated with corticosteroids at a dose of 1 mg/kg. Since there was no improvement in symptoms with corticosteroid therapy, the cranial MRI of the patient was evaluated as enlargements of Virchow-Robin spaces in the neuroradiology council.

Discussion: The enlargement of these perivascular spaces has been attributed to pathologies in arterial vessels such as advanced age, hypertension, and atherosclerotic carotid plaques, as well as fluctuations observed in the pulse. It has been reported that these enlargements are more commonly seen in the basal ganglia and the centrum semiovale. In our case, although cerebral amyloid angiopathy was considered prominent, no response was obtained to corticosteroid treatment. Upon evaluation of MRI lesions as enlargements of Virchow-Robin spaces in the neuroradiology council, it was deemed valuable to present the case in order to emphasize that these enlargements of perivascular spaces may lead to an increased risk of dementia.

Keywords: Virchow-Robin spaces, Dementia, Enlargement

GİRİŞ

İnsan beyni toplam vücut kütlesinin yalnızca %2'sini oluşturmasına rağmen vücut enerjisinin %20'sini tüketir. Beyin bu kadar yüksek enerji talebi ile yüksek miktarda protein, lipid, amiloid beta, tau ve modifiye kolesteroller olmak üzere çeşitli metabolitler atıklar da üretmektedir. Vücutta lenfatik sistem metabolik atıkları ortadan kaldırır ancak beyin parankiminde bu sistem bulunmaz. Beyinde metabolik atıkların temizlenmesini sağlayan sisteme glimfatik sistem adı verilmektedir. Bu sistem pia'ya nüfuz eden arteriyollerin etrafındaki perivasküler boşlukta 50 μm/s'lik konvektif akıştan oluşur, interstisyel sıvı boşluğa girerek venüllerin perivasküler boşluğuna boşaltılır ve metabolik atıkları da beraberinde taşır. Virchow-Robin boşlukları olarak bilinen perivasküler boşluklar, metabolik atıkları temizlemek için beyin omurilik sıvısı (BOS) ve interstiyel sıvının astrositik aquaporin 4 (AQP4) kanalları yoluyla değişimine izin vermektedir.[1] Bu boşlukların kritik rolleri enerji substratlarının değişimi, beyin immun sisteminin devamlılığı ve interstisyel amiloid betanın temizlenmesidir. Glimfatik sistemde bu perivasküler boşlukların mekanizmasında ortaya çıkan aksamalar, nörodejeneratif hastalıkların oluşum mekanizmalarından biri olarak gösterilmektedir. Virchow-Robin boşluklarındaki genişlemeler, beyaz cevher hiperintesiteleri ve serebral mikroenfarktlar gibi küçük damar hastalığı bulguları ile ilişkili gösterilmiştir. Bu perivasküler boşlukların genişlemesi ileri yaş, hipertansiyon, aterosklerotik karotis plağı varlığı

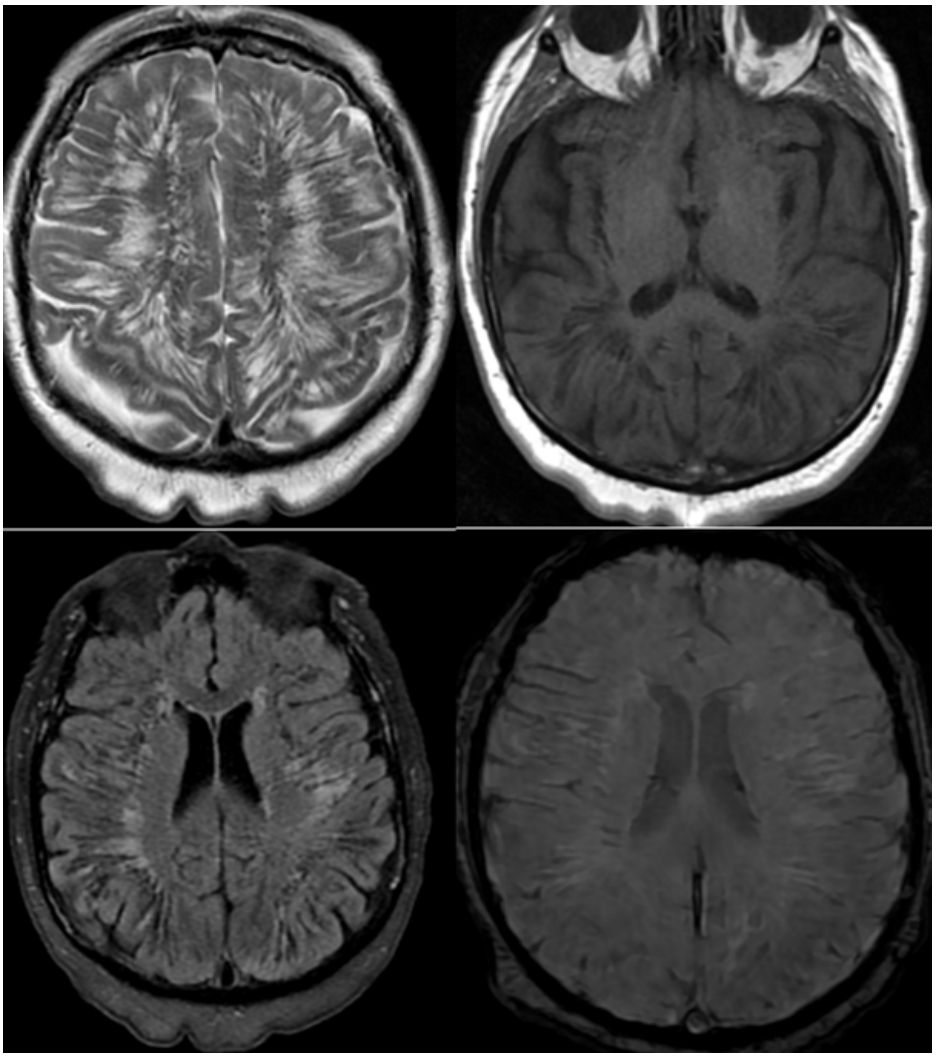
ile de ilişkilendirilmiştir.[2] Bu yazımızda demansiyel süreç ile takip edilen, nörogörüntülemesinde genişlemiş Virchow-Robin boşlukları saptanan, nadir görülen bir olguyu sunmayı amaçladık.

OLGU

Seksen yaşında kadın hastanın yaklaşık altı yıl önce başlayan ve giderek artan unutkanlık şikayetleri olduğu öğrenildi. Şikayetlerin basit düzeyde isimleri unutma ile başladığı, adres karıştırma, kendi işlerini görememe, kendi yemeğini yapamama ve idrar kaçırma şeklinde ilerlediği öğrenildi. Yaklaşık son iki yıldır halüsinasyonlar görmeye başladığı da ifade edildi. Özgeçmişinde Alzheimer tipi demans ön tanısı ile ginkgo biloba yaprakları kuru ekstresi, idrar kaçırma şikayeti için fesoterodin fumarat ve esansiyel tremor için de propranolol kullandığı öğrenildi. Nörolojik muayenesinde genel durum iyi, şuuru açık, koopereydi, kişi ve zaman dezoryanteydi. Konuşma spontan akıcı ve ense sertliği yoktu. Pupiller izokorik, IR +/+, göz hareketleri serbest, fasiyal asimetri yok ve kas gücü bilateral tamdı. Taban cilt refleksi bilateral fleksördü. Laboratuvar değerlerinde anlamlı değişiklik izlenmedi. Toplam 30 puanlık mini mental test 13 puan saptandı. Kranial manyetik rezonans görüntüleme (MRG) de her iki serebral hamisferde yaygın perivasküler genişleme ve T2 hiperintensiteleri ve konveksite düzeyinde mikrohemoraji odakları izlendi (Resim-1).

Resim 1.

Kranial MRG T2, T1, flair, swı kesitlerde izlenen Virchow-Robin boşlukları genişlemeleri



Dört yıl önce de çekilen kranial MRG da perivasküler genişlemeler izlendi. Serebral amiloid anjiopati ön tanısı ile interne edildi ve 1 mg/kg dan kortikoteroid tedavisi verildi. Kortikosteroid tedavisi ile semptomları gerilemeyen olgunun kranial MRG'si nöroradyoloji konseyinde Virchow-Robin boşluklarının genişlemeleri olarak değerlendirildi.

TARTIŞMA

Vasküler kognitif bozukluk; ağırlıklı olarak serebrovasküler hastalığın neden olduğu bir antitedir. Vasküler iskemik veya hemorajik etiyolojinin neden olduğu hafif bilişsel bozukluktan, vasküler demansa kadar geniş bir bilişsel bozukluk yelpazesini içerir[3]. İnme dünya çapında önemli morbidite ve mortalite nedenidir ve en sık olarak iskemik inme olarak görülmektedir.[4] Etyolojide ek olarak serebral küçük damar hastalığı, büyük arter aterosklerozu, kardiyoembolizm ve diğer daha az yaygın inme etiyolojileri yer alır.[3] Küçük damar hastalığıda inme, demans, intrakranial hemoroji, psikiyatrik hastalıklar gibi birçok olumsuz durumla ilişkilendirilmekte ve önemli bir toplumsal sorun olarak değerlendirilmektedir.[5] Virchow-Robin boşlukları denilen perivasküler boşlukların genişlemelerine ait beyaz cevher hiperintensiteleri ve serebral mikroinfarktlar diğer küçük damar hastalıkları belirteçleri ile yüksek oranda ilişkili bulunmuştur. Bu perivasküler boşlukların genişlemesi yüksek olasılıkla ileri yaş, hipertansiyon ve aterosklerotik karotis plakları gibi arteryel damarlardaki patolojiler ve nabızda izlenen dalgalanmalar ile açıklanmaya çalışılmıştır. Bu mekanizmalara ek olarak beyin atrofisi, inflamasyon ve perivasküler akışın fonksiyon bozuklukları da düşünülmektedir. Matthew ve arkadaşlarının 2021 yılında 72 ve 92 yaş arasında 414 hasta ile yaptıkları bir çalışmada perivasküler boşlukların genişlemelerinin, küçük damar hastalığının diğer belirteçlerinden bağımsız olarak 4 yıl boyunca genel bilişsel aktivitede bozulma ve 8 yıllık takipte demans riskinde 2,9 kat artışla ilişkili olduğu bildirilmiştir.[6] Bizim olgumuz seksen yaşındaydı, semptomları altı yıl içinde ilerlemişti ve kranial MRG da perivasküler genişlemeler izlendi. Yine aynı çalışmada perivasküler boşluklardaki bu genişlemelerin daha çok bazal ganglionlar ve sentrum semiovalede görüldüğü bildirilmiş ve bazal ganglion genişlemelerinin daha çok hipertansiyonla ilişkili patolojilere, sentrum semiovaledeki genişlemelerinde daha çok amiloid anjiopati ile ilişkili Alzheimer hastalığına neden olabileceği bildirilmiştir.[6] Virchow-Robin boşlukları tipik olarak bulundukları yere göre üçe ayrılır; Tip 1 boşluklar genellikle 2 mm'den daha büyük çaplı olup, ön komissürden bazal ganglion içine giren lentikülostriat arterlerle ilişkilidir. En yaygın olan tip 2 boşluklar genellikle medüller arterlerin kortikal gri maddeyi delerken büyük konveksiteden beyaz maddeye uzandığı yerlerde bulunur ve tip 3 boşluklar orta beyinde bulunur ve pontomezensefalik kavşakta kolliküler arter ve yardımcı kolliküler arter dallarını sarmalar.[6] Normalde bu Virchow-Robin boşluklarının boyutları 2 mm'den küçüktür ve 2 mm ve üzeri boyutları genişlemiş olarak kabul edilmektedir. Bu perivasküler boşlukların genişlemelerinin multiple skleroz dâhil diğer nöroinflamatuar hastalıklarla da ilişkisi gösterilmiştir. [7] Etemadifar ve arkadaşları 73 MS hastası ile yaptıkları bir çalışmada MS hastalarında normal sağlıklı bireylere göre Virchow-Robin boşluklarının daha fazla görüldüğünü bildirmişlerdir.[8] Vivash ve arkadaşlarının yakın zamanda 142 MS hastası ile yaptıkları bir çalışmada kontrast tutan MS lezyonları çıkmadan önce Virchow-Robin boşluklarının hacminde artış olduğu ve inflamasyonla ilişkisinin perivasküler boşlukların içinde bağışıklık hücrelerinin lokal birikimine bağlı olabileceği bildirilmiştir[9]. Glimfatik sistemin bir parçası olan Virchow-Robin boşluklarının genişlemeleri vasküler kognitif bozuklardan

vasküler demansa ve MS gibi nöroinflamatuar hastalıklara kadar geniş bir yelpaze ile ilişkilendirilmiştir.[7] Bizim olgumuzda son altı yılda belirginleşen demansiyel semptomları ile tarafımıza başvurmuş ön planda amilod anjiopati de düşünülsede kortikosteroide tedavi yanıtı alınamamıştır. Nöroradyoloji konseyinde MRG lezyonlarının Virchow-Robin boşluklarının genişlemesi lehine değerlendirilmesi üzerine, bu perivasküler boşlukların genişlemelerinin demans riskinde artışa neden olabileceğini vurgulamak amacıyla sunulmuştur.

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Letter to the Editor

Overview of Prognosis of FLT3 Mutations and Interactions with Other Genetic Alterations in Acute Myeloid Leukemia

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Acute Myeloid Leukemia (AML) is one of the most aggressive hematological malignancies. It has a highly heterogeneous genetic background and complex clonal evolution. In this letter, we emphasized the prognostic importance of a crucial biomarker in AML – the Fms - like tyrosine kinase 3 (FLT3). This receptor tyrosine kinase plays a significant role in several cellular signalling processes. FLT3 is found on hematopoietic stem cells and early progenitor cells. After binding to its ligand, activated FLT3 triggers intracellular kinase, leads to cellular proliferation, and inhibits differentiation and apoptosis.[1]

Almost 30% of newly diagnosed AML patients, including adults and children, have activating mutations in the FLT3 gene. FLT3 mutations fall into two main categories: internal tandem duplication (ITD) insertion in the juxtamembrane domain and point mutations in the tyrosine kinase domain (TKD), which mostly affect residue D835 (D835Y, D835H, D835V, e.g.). Rare FLT3 point mutations are also found in TKD. These include F594L, K663Q, N841I, and Y842C. FLT3-ITD occurs in almost 25% of AML cases, while TKD mutations occur in nearly 5%.[2]

FLT3 mutations, also associated with other recurrent mutations and cytogenetic abnormalities, are particularly associated with the nucleophosmin 1 (NPM1) gene mutation, found in 50-60% of cases.[3] According to the 2022 ELN criteria, FLT3wt - NPM1mut is favorable while FLT3-ITD - NPM1mut and FLT3-ITD - NPM1wt are intermediate prognosis markers.[4] FLT3 mutations have also been reported in approximately 16% of AML patients with t(8;21)(q22;q22) (RUNX1/RUNX1T1). Among patients with this combination, those with a high FLT3-ITDmut allele burden (>50%) have been reported to have a lower survival risk, while those with a high FLT3-TKDmut allele burden have a better prognosis; however, there are conflicting results in the literature.[5] FLT3-ITD mutations have been associated with a worse prognosis than TKD mutations. A direct correlation between the duplication size in FLT3-ITD mutations and chemotherapy resistance has been reported. However, the prognostic utility

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of high FLT3-ITD allele burden has been removed from the updated ELN 2022 guidelines. DNMT3A, TET2, PTPN11, NRAS gene mutations are also found together with FLT3 mutations, but there is not enough evidence to say whether they are prognostically favorable or unfavorable. FLT3 mutations and ASXL1, WT1, and RUNX1 mutations have been associated with poor prognosis. Most cytogenetic markers of good or poor prognosis have not been reported to be affected by FLT3 mutations.[3]

FLT3 inhibitors have now become pivotal in treating FLT3-mutated AML. Type I (midostaurin, gilteritinib, andcrenolanib) and type II inhibitors (quizartinib and sorafenib) targeting FLT3 have been developed.[2] Chemotherapy plus FLT3 inhibitor treatments in AML are ongoing in newly diagnosed patients. However, further studies are needed to clarify the algorithms, especially for patients with additional genetic alterations. We believe this letter will help clinicians in the evaluation of FLT3 mutations alone and combined with other genetic alterations in AML. Hopefully, it will be an inspiration for new studies in AML.

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