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Relationship between fortilin levels and coronary ischemia in heart failure

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ABSTRACT

Objectives: Fortilin is a multifunctional protein that protects cells against apoptosis. We aimed to investigate the levels of fortilin in patients with heart failure.
Methods: Patients with ejection fraction (EF) below 40% were divided into two groups according to coronary angiography results: those with ischemic heart failure (Group 1) and those with non-ischemic heart failure (Group 2). Patients with normal anatomy and EF over 50% were included in the control group (Group 3).
Results: A total of 119 patients were prospectively included in the study. A total of 81 patients (41 patients with ischemic heart failure and 40 patients with non-ischemic heart failure) were included in the heart failure group. 38 patients with EF >50 and normal coronary anatomy were included in the control group. There was no significant difference in serum fortilin levels between the study groups (Group 1: 5.5±2.6 ng/mL, Group 2: 6.1±3.8 ng/mL, and Group 3: 5.6±3.6 ng/mL; P=0.693). Fortilin did not show a correlation with any other variables.
Conclusion: In our study, there was no significant difference in fortilin levels between the groups, and no relationship was found between coronary ischemia and fortilin levels in heart failure.
Keywords: Heart failure, fortilin, ejection fraction, pro-BNP

Cellular changes, apoptosis, and various factors also play a role in the pathogenesis of heart failure. In the early stages of heart failure, cardiac physiology attempts to adapt through several compensatory mechanisms to maintain cardiac output and meet systemic demands. With increased wall tension, the myocardium tries to compensate for the loading findings that increase wall tension and deterioration through cardiac remodeling. This paradoxical need for increased cardiac output eventually leads to myocardial cell death and apoptosis to meet myocardial demand. As apoptosis continues, the reduction in cardiac output with increased demand leads to an ongoing cycle of increased neurohumoral stimulation and maladaptive hemodynamic and myocardial responses [1]. Only recently has slowing or reversing remodeling become a goal of treatment for capillary insufficiency. Left ventricular diastolic and end-systolic volume and EF data; it support the beneficial effects of therapeutic agents such as angiotensin-converting enzyme inhibitors and beta-adrenergic blocking agents on the remodeling process. These agents also provide benefits in terms of morbidity and mortality [2].

Pathological remodeling may occur following

pressure overload, volume overload, or cardiac injury and may be localized or widespread depending on etiology. In each of these processes, remodeling can change from a compensatory process to a maladaptive one. Other components include the interstitium, fibroblasts, collagen, and the coronary vasculature. Remodeling and myocyte hypertrophy are associated with a series of cellular changes that underlie structural remodeling, including myocyte loss due to apoptosis or necrosis, fibroblast proliferation, and fibrosis [3].

Many forms of myocardial remodeling are associated with increased expression of fetal heart-specific genes. Additionally, post-translational modifications can affect protein function and quantity, altering many aspects of cellular homeostasis. Fortilin, also called histamine-releasing factor, is a 172 amino acid polypeptide that was originally reported to be abundantly expressed in tumor cells. Fortilin is considered to be present in the cytosol, nucleus, mitochondria, and blood and plays a crucial role in normal physiological function. It has been reported to protect cells against apoptosis and promote cell proliferation. First, fortilin binds to a tumor suppressor protein (p53). Binding both destabilizes the protein and prevents it from transcriptionally activating pro-apoptotic molecules such as B-cell lymphoma gene 2-related proteins [4-7].

Fortilin directly binds to and negatively regulates tumor suppressor protein 53 and endoplasmic reticulum stress processing protein (IRE1α), both of which promote cardiomyocyte loss and subsequent capillary rarefaction. Second, fortilin cooperates with B-cell lymphoma gene 2 family proteins to inhibit apoptosis. It binds to the anti-apoptotic myeloid cell leukemia 1, a B-cell lymphoma gene 2 family protein. Fortilin also binds another anti-apoptotic B-cell lymphoma 2 protein and protects against apoptosis. Third, fortilin binds calcium, clears it intracellularly, sequesters it, and protects cells against calcium-dependent apoptosis. Fortilin exhibits cytokine-like functions, including histamine release, induction of cytokines and chemoattractants, enhancement of B cell proliferation, and immunoglobulin production during late-phase allergic inflammation [8-10]. Fortilin expression increases in human atherosclerotic lesions. Previous studies demonstrated that fortilin-deficient mice developed decreased atherosclerotic lesions associated with increased macrophage apoptosis, and decreased

macrophage infiltration [11]. Fortilin may contribute to the progression of atherosclerosis. Blood fortilin levels were suggested to be a promising biomarker for apoptosis [12]. Heart failure is associated with apoptosis. Preventing apoptosis may be effective in the treatment and progression of heart failure. Perhaps, due to low fortilin levels, heart failure may progress faster in some patient groups and the prognosis may be worse. For this purpose, in this study, we aimed to examine fortilin levels in chronic heart failure patients.

METHODS

Patients presenting to our institution's outpatient clinic were prospectively enrolled. Patients with ischemic and non-ischemic heart failure who had undergone coronary angiography were included. Healthy individuals with no significant lesions on coronary angiography were included as the control group. Detailed cardiovascular examination and transthoracic echocardiography were performed for each patient during the outpatient evaluation. Demographic data were recorded. Blood pressure was measured in all patients, followed by fasting morning blood samples. Patients with ejection fraction (EF) below 40% were divided into two groups according to coronary angiography results: those with ischemic heart failure (Group 1) and those with non-ischemic heart failure (Group 2). Patients with left ventricular ejection fraction less than 40% on echocardiography and coronary artery stenosis less than 50% on coronary angiography were included in Group 2. Patients with normal anatomy and EF over 50% were included in the control group (Group 3). Three groups were formed with individuals aged between 18 and 75 years, ensuring similar gender and age characteristics. The GE Vivid S5 echocardiography machine was used for transthoracic echocardiographic evaluation of the patients. The Modified Simpson method was used to obtain quantitative results in evaluating left ventricular dimensions, mass, and contractile functions. EF values were calculated using this method.

Exclusion criteria were as follows: patients with LVEF between 40-50%, rheumatic diseases, acute inflammation, liver and kidney failure (patients with glomerular filtration rate <15 mL/h), patients with thyroid hormone disorders, the first 40 days after acute

myocardial infarction, the first 90 days after bypass and percutaneous coronary intervention, left ventricular hypertrophy, moderate-to-severe aortic and mitral stenosis, history of prosthetic valve surgery, chronic obstructive pulmonary disease, asthma, lung parenchymal diseases, and patients with a history of stroke.

Fortilin Analysis Method and Levels

Samples were centrifuged at 2500 rpm for 15 minutes. The obtained serum samples were aliquoted into microcentrifuge tubes and stored at -80°C until the day of analysis. On the day of the study, samples were brought to room temperature. Serum fortilin levels were measured using a commercial kit and the ELISA (Enzyme-Linked Immunosorbent Assay) method. Mass measurements were made using the ELISA principle.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 20 (IBM Corp., Armonk, NY, USA). Numerical variables were presented as mean ± standard deviation or median (min-max), and categorical variables were presented as number and percentage (n, %). Whether the variables followed a normal distribution was evaluated using the Kolmogorov-Smirnov test. For three-group comparisons, parametric variables with normal distribution were evaluated using ANOVA, while non-parametric variables with normal distribution were evaluated using the Kruskal-Wallis test. If there was a difference between the three groups in the ANOVA test, the Tukey test was used for pairwise comparisons between groups. In the Kruskal-Wallis test, if there was a difference between the three groups in non-parametric variables, Dunn's test was used, and categorical variables were compared using the Chi-square test. The Bonferroni test was used for pairwise comparisons in categorical tests. Variables with differences between groups were included in correlation analysis to investigate the correlations of pro-BNP and fortilin. A P-value <0.05 was considered statistically significant.

RESULTS

A total of 119 patients were prospectively included in the study. A total of 81 patients (41 patients with is-

chemic heart failure and 40 patients with non-ischemic heart failure) were included in the heart failure group. Thirty-eight patients with EF >50 and normal coronary anatomy were included in the control group. There was no difference in gender, body mass index, diabetes, smoking status, and family history rates between the groups (Table 1). However, patients in the control group were younger (Group 1: 65.3±4.6, Group 2: 63.5±10.8, and Group 3: 55.3±10.1; P<0.001). There was a difference in hypertension between the ischemic heart failure and control groups (Group 1: 31 [75.6%], Group 2: 24 [60%], and Group 3: 18 [47.4%]; P=0.035). The rates of atrial fibrillation were similar between both heart failure groups but significantly lower in the control group (Group 1: 10 [24.4%], Group 2: 13 [32.5%], and Group 3: 1 [%2.6]; P=0.003). In terms of medical treatment, the use of beta-blockers, mineralocorticoid receptor antagonists or angiotensin receptor blockers and diuretics was higher in group 1 than in the other groups. Additionally, statin use was higher in group 1 because the patient had coronary artery disease. In groups 1 and 2, EF and Tricuspid Annular Plane Systolic Excursion (TAPSE) were lower, while left ventricular diameters and Left Ventricular Mass Index (LVMI) were higher compared to the control group (Table 2).

There were significant differences in urea, creatinine, pro-BNP, and CRP levels between both heart failure groups and the control group (Table 3). There was no significant difference in serum fortilin levels between the study groups (Group 1: 5.5±2.6, Group 2: 6.1±3.8, and Group 3: 5.6±3.6; P=0.693). Fortilin did not show a correlation with any other variables. A moderate positive correlation was observed between Pro-BNP and GFR, creatinine, low-density lipoprotein cholesterol (LDL-C), left ventricular systolic diameter (LVSD), and left ventricular diastolic diameter (LVDD) (Table 4).

DISCUSSION

In our study, Fortilin was found to be similar in heart failure and normal individuals. When compared between patient groups, although urea, glomerular filtration rate, and creatinine values were slightly higher in the ischemic heart failure groups, this did not affect fortilin levels. Although mild increases in urea and cre-

Table 1. Clinical characteristics of study groups

Variables	Ischemic HF Group (n=41)	Non-ischemic HF Group (n=40)	Control Group (n=38)	P value
Age (years)	65.3±4.6	63.5±10.8	55.3±10.1	**<0.001**
Male, n (%)	32 (78)	25 (62.5)	21 (55.3)	0.090
Body Mass Index (kg/m²)	27.6±3.6	27.7±3.9	28.5±3.6	0.481
Diabetes, n (%)	23 (56.1)	18 (45)	13 (34.2)	0.148
Hypertension, n (%)	31 (75.6)	24 (60)	18 (47.4)	**0.035**
Smoking, n (%)	22 (53.7)	15 (37.5)	13 (34.2)	0.168
Family History, n (%)	11 (26.8)	7 (17.5)	3 (7.9)	0.090
HF Duration (years)	5 (2-20)	4.2 (1-10)	-	0.203
Functional capacity, NYHA	1.8±0.8	2.0±0.9	-	0.921
AF, n (%)	10 (24.4)	13 (32.5)	1 (2.6)	**0.003**
Medications				
Beta-blocker, n (%)	40 (97.6)	30 (75)	23 (60.5)	**<0.001**
Digoxin, n (%)	5 (12.2)	7 (17.5)	-	0.502
ACEI and ARB, n (%)	31 (75.6)	23 (57.5)	19 (50)	0.054
Diuretic, n (%)	30 (73.2)	23 (57.5)	3 (7.9)	**<0.001**
MRA, n (%)	24 (58.5)	22 (55)	1 (2.6)	**<0.001**
Anticoagulant, n (%)	11 (26.8)	13 (32.5)	2 (5.3)	0.009
Antiplatelet, n (%)	33 (80.5)	30 (75)	30 (78.9)	0.521
Sacubitril-valsartan, n (%)	4 (9.8)	9 (22.5)	-	0.118
SGLT2 inhibitors, n (%)	3 (7.3)	6 (15)	2 (5.3)	0.290
Statin, n (%)	33 (80.5)	20 (51.3)	27 (71.1)	**0.018**

ACEI=Angiotensin-Converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker, AF=Atrial fibrillation, HF=Heart Failure, MRA=Mineralocorticoid Receptor Antagonist, SGLT2=Sodium-Glucose Cotransporter 2 Inhibitor

Table 2. Comparison of echocardiographic and angiographic variables among groups

Variables	Ischemic HF group (n=41)	Non-ischemic HF group (n=40)	Control group (n=38)	P value
EF (%)	34 (24-40)	31.5 (15-40)	59.9 (50-70)	**<0.001**
Left ventricular diastolic diameter (cm)	58±6.2	58±7.7	46.4±3.7	**<0.001**
Left ventricular systolic diameter (cm)	47.2±8	47±7.6	31.4±4.3	**<0.001**
TAPSE (mm)	18.6±2.9	19.3±4.1	25±4	**<0.001**
LVMI (g/m²)	204±76	131±29	112±39	**<0.001**
Systolic pulmonary artery pressure (mmHg)	35±12	31±13	--	0.317

EF=Ejection Fraction, HF=Heart Failure, TAPSE=Tricuspid Annular Plane Systolic Excursion, LVMI= Left Ventricular Mass Index

Table 3. Comparison of biochemical and hematological variables among groups

Variables	Ischemic HF Group (n=41)	Non-Ischemic HF Group (n=40)	Control Group (n=38)	P value
Fasting blood sugar (mg/dl)	102 (66-392)	105 (67-210)	103 (75-181)	**0.046[b,c]**
Urea (mg/dl)	42±12.5	37.5±12.5	31.2±10.4	**<0.001[b]**
GFR	72±21	75±24	93.9±22.6	**<0.001[b,c]**
Creatinine (mg/dl)	1.04±0.3	0.9±0.3	0.85±0.18	**0.009[b]**
Total Cholesterol (mg/dl)	159±39	164±49	176±40	0.200
HDL Cholesterol (mg/dl)	44±11	44±13	48±11	0.209
LDL Cholesterol (mg/dl)	80±31	93±37	102±36	**0.019[b]**
Triglycerides (mg/dl)	152±15	136±71	128±53	0.268
CRP (mg/dl)	5.5 (2.6-10.5)	10.2 (0-59.5)	3.5 (0.3-20)	**0.015[c]**
Uric Acid (mg/dl)	5.9±1.8	6.3±2.5	5.07±1.4	**0.018[c]**
Hemoglobin (mg/dl)	13.1±1.7	13.4±3.4	13.3±1.9	0.857
Hematocrit (%)	40±4.5	39±4.2	40±5.5	0.374
Platelet Count (n)	242±52	221±49	233±51	0.205
Pro-BNP (ng/mL)	892 (20-8750)	2752 (10-35000)	104 (10-852)	**<0.001[b,c]**
Fortilin (ng/mL)	5.5±2.6	6.1±3.8	5.6±3.6	0.693
HbA1c (mmol/mol)	7±1.6	6.3±1.6	5.6±0.7	**<0.001[b,c]**

BNP=Brain Natriuretic Peptide, CRP=C-Reactive Protein, HF=Heart Failure, LDL-C=Low-Density Lipoprotein Cholesterol, GFR= Glomerular Filtration Rate, HDL-C= High-Density Lipoprotein Cholesterol

[a]difference between ischemic heart failure and non-ischemic heart failure groups (P<0.05)

[b]difference between ischemic heart failure and control group (P<0.05)

[c]difference between non-ischemic heart failure and control group (P<0.05)

atinine are expected in heart failure, we thought that this difference was not of clinical importance because we excluded patients with a glomerular filtration rate below 15 in our study. Additionally, HbA1c levels were slightly higher in the ischemic vascular insufficiency group. We thought that this was because diabetes is an important CAD risk factor and we evaluated that blood sugar control was not better in the ischemic vascular insufficiency group. Interestingly, Pro-BNP values were higher in the non-ischemic vascular insufficiency group than in the ischemic vascular insufficiency group. As it is known, heart failure worsens in the presence of atrial fibrillation. We attributed this increase in the non-ischemic heart failure group to the higher atrial fibrillation rates in this group. There are no studies on blood levels of fortilin in the literature on heart failure. When we started the study, we assumed that it might affect slowing down car-

diomyocyte loss, as far as we understood from animal experiments [11]. Interestingly, fortilin did not correlate with any study parameters. However, in clinical studies, fortilin is expected to reduce cardiomyocyte loss due to its anti-apoptotic properties. We did not see this effect. The fact that fortilin is incompatible with other cardiological parameters makes us think that more detailed studies should be conducted on fortilin. That's why we did a study, but we couldn't find a relationship. If fortilin correlated with pro-BNP, it would make our study meaningful. However, there was no correlation between them. Fortilin also did not correlate with EF and heart diameters. As is known, chronic heart failure is the main cause of programmed death. Factors that trigger programmed death are important. Although fortilin is expected to slow programmed death, no data is showing this in clinical trials. Interestingly, triggering properties of fortilin have been de-

Table 4. Correlation of Pro-BNP and fortilin with other variables

Variable	Pro-BNP		Fortilin	
	r	P value	r	P value
Age	0.088	0.586	0.006	0.970
Fasting blood sugar	-0.062	0.702	-0.118	0.462
Urea	0.226	0.156	-0.125	0.438
GFR	0.468	**0.002**	0.028	0.864
Creatinine	0.355	**0.023**	-0.111	0.490
LDL-C	0.524	**<0.001**	0.247	0.120
C-reactive protein	0.237	0.136	-0.174	0.276
Uric Acid	0.148	0.357	0.200	0.209
HgA1C	-0.030	0.852	-0.154	0.335
TAPSE	-0.364	0.019	-0.038	0.812
LVMI	0.047	0.770	0.029	0.859
LVSD	0.383	**0.013**	0.072	0.653
LVDD	0.368	**0.018**	0.008	0.959
EF	-0.199	0.299	-0.123	0.443
Fortilin	-0.072	0.654	-	-

EF=Ejection Fraction, LDL-C=Low-Density Lipoprotein Cholesterol, GFR=Glomerular Filtration Rate, LVSD=Left Ventricular Systolic Diameter, LVDD=Left Ventricular Diastolic Diameter, LVMI=Left Ventricular Mass Index, TAPSE=Tricuspid Annular Plane Systolic Excursion, HgA1C=Glycated hemoglobin A1C

tected in hypertension and atherosclerosis [13, 14]. This is a confusing situation.

The groups were determined as ischemic vascular insufficiency, non-ischemic vascular insufficiency, and control group. Although care was taken to ensure that the individuals included in the groups were balanced in terms of demographic characteristics, the vascular insufficiency groups were more balanced in terms of demographic characteristics, while the age was younger and the rates of atrial fibrillation and hypertension were lower in the control group. Including gender-balanced numbers of individuals in both heart failure groups proved challenging. One of the difficulties encountered in patient selection was that connective tissue diseases were accepted as exclusion criteria in individuals in the non-ischemic vascular insufficiency group.

Limitations

Although the patient group in our study was small, the lack of a relationship does not reduce the value of our study. For this reason, it is thought that more detailed histopathological studies are needed rather than clinical studies to evaluate the relationship of fortilin with vascular insufficiency.

CONCLUSION

There was no significant difference in fortilin levels between the groups, and no relationship was found between coronary ischemia and fortilin levels in heart failure. Further studies with larger sample sizes are needed to investigate the role of fortilin in heart failure pathophysiology and its potential as a therapeutic target.

Ethics Committee Approval

This study was approved by Tekirdağ Namık Kemal University, Non-invasive Clinical Research Ethics Committee (Decision No: 2921.277.11.21, Date: 30.11.2021)

Authors' Contribution

Study Conception: ŞA; Study Design: ŞA; Supervision: AD, CA; Funding: N/A; Materials: SG; Data Collection and/or Processing: SG; Statistical Analysis and/or Data Interpretation: AD, CA; Literature Review: AD, SG; Manuscript Preparation: AD, CA and Critical Review: ŞA, CA, AD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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ADMA, neutrophil to lymphocyte, platelet to lymphocyte ratios and phase angle: effects on inflammation and nutrition in hemodialysis patients

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ABSTRACT

Objectives: Neutrophil/lymphocyte ration (NLR) and platelet/lymphocyte ratio (PLR) levels can be used as systemic infallamotory parameters. Asymmetric dimethyl arginine (ADMA) inhibits endothelial nitric oxide synthase. Phase Angle (PhA) is a potential paremeter to screen for inflammatory abnormalities. In present study we aimed to determine the relations between NLR, PLR, ADMA, and PhA in terms of early markers for nutritonal status in addition to their well-known role in inflammation.

Methods: A total of 89 patients undergoing maintenance hemodialysis 3 days a week at least 6 months were enrolled. To assess nutritional status, we performed the dietary questionnaire and mini nutritional assessment score (MNAS). ADMA was measured by ELISA. NLR and PLR are calculated from monthly complete blood count tests. Patients were divided into 2 groups accordng to NLR levels as group 1 (NLR≥4.6; n=48) ve and group 2 (NLR<4.6, n=41).

Results: The mean ADMA level was 0.03±0.01 µmol/L, the mean PhA was 7.2±1.1°. In subgroup analysis, MNAS, albumin levels and phase angle of patients in group 1 were lower and CRP, PLR, ADMA levels were higher when compared to group 2. In correlation analysis, NLO was positively correlated with PLR, CRP and ADMA however negatively correlated with albumin and PhA levels. In regression analysis, NLR, PLR and ADMA were detected as independent predictors of MNAS.

Conclusion: In conclusion our study suggests that NLR, PLR and ADMA are independent predictors for nutritional status and inflammation in patients ongoing hemodialysis.

Keywords: ADMA neutrophil, lymphocyte, platelet, phase angle, inflammation, nutrition, hemodialysis

Maintenance hemodialysis (MHD) is the most applied treatment option for end stage kidney disease [1]. Previous studies have shown that inflammation could be resulted as malnutrition in this population [2]. Several factors as inadequate food intake, uremic toxins, comorbid diseases, the dialysis procedure, inflammatory conditions are all involved in the development of malnutrition [3]. The prevalence of malnutrition varies up to 76% in MHD patients and considered significantly important for morbidity and mortality of this population [4].

Neutrophil to lymphocyte ratio (NLR) is an inflammatory parameter that shows the presence of systemic inflammation [5]. Previous reports have shown

that NLR plays a significant role in the development of arteriosclerosis [6, 7]. Besides studies also reported that NLR in MHD patients was related to malnutrition [8]. Platelet to lymphocyte ratio (PLR) is another parameter that is associated with inflammation in patients on MHD [9].

Asymmetric dimethyl arginine (ADMA) is competitive inhibitor of endothelial nitric oxide synthase [10]. Phase angle (PhA) by bioimpedance analysis is an alternative approach for inflammation [11].

In present study we aimed to determine the relations between NLR, PLR, ADMA and PhA in terms of early markers for nutritonal status in addition to their well-known role in inflammation.

METHODS

This is a cross-sectional, observational, single-center study aimed to analyze the relationship between inflammation, malnutrition, ADMA, neutrophil to lymphocyte, platelet to lymphocyte ratios and phase angle in MHD patients. Among 130 MHD patients, 89 patients were selected according to following exclusion criteria: (1) lack of regular follow-up, (2) history of chronic inflammatory disease of unknown origin, (3) Kt/V<1.4, (4) active systemic infection or hospitalization in last 3 months, (5) active gastrointestinal disorders, (6) history of peripheral artery disease, (7) active smoking, and (8) history of malignancy. The study was approved by Baskent University Institutional Review Board and Ethics Committee (KA13/245, 12/02/2013). All patients gave informed consent for this study.

Biochemical Assays

All patients' demographical, clinical, and biochemical parameters were analyzed. Venous blood samples were taken after an overnight fast. All blood samples were collected pre dialysis [8]. Lipid profile was measured every 6 months, glycosylated hemoglobin (HbA1C; by high-performance liquid chromatography) levels were measured every 3 months and serum fasting plasma glucose (FPG), uric acid, creatinine, C-reactive protein (CRP), calcium, phosphorus, albumin levels, and complete blood count were measured in monthly periods. NLR and PLR levels were calculated from montly complete blood count parameters.

Serum ADMA levels were measured by ELISA method by using an Immunodiagnostic human ADMA kit.

Nutritional Status Assessment

The dietary survey was performed with 3-day dietary histories recorded in a self-completing food diary. The Mini Nutritional Assessment Score (MNAS) includes 18 questions [12].

Phase Angle (PhA) Measurement

After measurement of body weight and height, body composition was measured using the Tanita. Four electrodes were placed on the right hand and foot on the side c ontralateral to the arteriovenous fistula (if present) of the supine patient. Two electrodes were dorsally placed on the hand: inthemetacarpophalangeal articulations and in the corpus, 5cm apart. The pair on the foot were located in the metatarsophalangeal and in the articulation, 6 cm apart. The following were determined: extracellular water (ECW), intracellular water (ICW), and PhA.

Patients were divided into 2 groups according to mean NLR cut-off level as group 1 (NLR$\geq$4.6; n=48) ve and group 2 (NLR<4.6, n=41).
All patients were anuric without any residual urine output which is the most important mortality indicator in this population.

Statistical Analysis

Statistical Package for Social Sciences (version 14.0; SPSS) was used. Kolmogorov-Smirnov test is used for distribution analysis. Normal distributions were expressed as mean (standard deviation). Related data were compared with paired samples t test. Categorical data were compared by χ^2 test, and P<0.05 was considered statistically significant.

RESULTS

This study evaluated 89 patients ongoing MHD. The etiology of CKD in MHD patients was as following: Type 2 DM 38%, hypertension 26%, glomerulonephritis 12%, ADPKD 8 %, and unknown 16 %.

Demographic data of MHD patients were as follows: Patients were 57 (47.8 %) males with mean of age of 58.1±4.8 years. The mean of BMI is 20.4±4.8 kg/m2. Duration of dialysis in MHD patients was 12.2±3.6 years. The mean NLR was 4.6±0,7, the mean PLR was 148.4±28.6, the mean CRP was 29.4±2.4 mg/L, the mean albumin level was 3.4±0.2 g/dL, the mean ADMA level was 0.4±0.01 µmol/L, the mean PhA was 7.2±1.1°.

According to MNAS of MHD patients, 18.4 % of patients had malnutrition, 42% of patients had risk of malnutrition and 39.6% of patients had normal nutritional status.

In subgroup analysis of study population, demographic data as age, gender, duration of dialysis BMI and ECW/ICW ratio were similar in 2 groups. The MNAS, albumin levels and PhA of patients in group 1 were significantly lower and CRP, PLR, ADMA levels were significantly higher when compared to group 2 (Table 1).

In correlation analysis, NLR was positively correlated with PLR, CRP and ADMA (r: 0.747, P=0.001, r: 0.534, P =0.003, and r: 0.342, P=0.001, respectively), however negatively correlated with albumin and PhA levels (r: -1.8, P=0.016, r: -1.4, P=0.014, respectively).

In regression analysis, NLR, PLR and ADMA were detected as independent predictors of MNAS (P=0.001, P=0.01, and P=0.02, respectively).

DISCUSSION

Inflammation plays an essential role in the development and progression of malnutrition in patiens ongoing hemodialysis. The peripheral blood cell analysis is preferred for prediction of inflammation and nutritional status [13]. Besides, ADMA is the most potent endogenous inhibitor of nitric oxide synthase and have an important role in inflammation [14]. PhA by is another parameter for inflammatory abnormalities especially in MHD patients.

In present study, we detected ADMA, NLR and PLR are important early markers for nutritional status in addition to their well-known role in inflammation in MHD patients. The incidence of malnutriton in MHD patients reaches up to 60 % in previous studies [15]. Inflammatory parameters as CRP are the most used marker for predicting malnutriton [16]. The negative correlation between inflammation parameters and serum albumin levels are also well known [17]. Recent studies have shown that NLR was also related

Table 1. Subgroup analysis of study population

	Group 1 (n=48)	Group 2 (n=41)	P value
Age (years)	57.4±3.8	59.2±4.4	0.05<
Gender			
Male (n)	31	26	0.05<
Body mass index (kg/m^2)	21.4±2.6	22.1±3.2	0.05<
CRP (mg/dL)	17.8±2.9	5.7±0.7	**0.01**
Albumin (g/dL)	3.1±0.8	3. ±0.4	**0.03**
NLR	4.9±0.2	4.1 ± 0.5	**0.01**
PLR	154.6±16.6	144.6±21.2	**0.03**
ADMA (µm/L)	0.4±0.01	0.28±0.03	**0.01**
MNAS	18. ±0.4	25.7±0.4	**0.01**
ECW/ICW	0.41±0.2	0.43±0.1	0.05<
PhA (º)	6.8±1.0	7.7±1.2	**0.02**

Data are shown as mean ±standard deviation or number (frequency). ADMA=Asymmetric Dimethylarginine, BMI=Body mass index, CRP=C-Reactive Protein, ECW=Extracellular water, ICW=Intracellular water, NLR=Neutrophil Lymphocyte Ratio, PLR=Platelet Lymphocyte Ratio, MNAS=Mini Nutritional Assessment Score, PhA=Phase Angle

to protein energy wasting. In present study, patients with higher NLR had lower albumin levels and nutritional status and higher inflammation levels as like previous studies. We agree with Malhotra et. al. [18] as leukocytes acts as principal effectors cell in the acute inflammation. Martinez et.al. [19] reported that NLR were significantly associated with nutritional status and inflammation. A recent study suggested that serum albumin was significantly decreased in MHD patients with malnutrition, and NLR was an independent risk factor for malnutriton [20]. In addition, they also demonstrated that NLR was negatively correlated with albumin levels as like present study. They identified these results with the increased NLR might reduce albumin levels, resulting in malnutriton. Our findings are consistent with the previous studies that albumin acts as a negative acute phase parameter in MHD patients.

An elevated PLR level is a novel inflammation marker in chronic kidney disease. In present study, we detected patients with lower nutritional status had higher values of PLR in addition to higher NLR and CRP. A recent study found that patients with poor nutritional status had higher levels of PLR than healthy population [21, 22]. Another study on non-dialysis patients with end stage renal disease detected that either NLR or PLR was positively correlated with CRP. Moreover, they concluded NLR can be an alternative parameter to predict inflammation than PLR in this population [23]. Okyay *et al*. [24] also detected significantly higher NLR in CKD patients than healthy population. Moreover, they showed the presence of higher NLR ratio in both pre-dialysis and dialysis patients, and significantly higher NLR was correlated with higher PLR in CKD patients [24] as like present study. Another study in CKD patients, couldn't detected a statistically significant correlation between SGA score and NLR, PLR, or CRP in patients' group. They showed both ratios of PLR and NLR were positively correlated to high CRP in CKD group when compared to healthy subjects. [25].

ADMA is shown to be a strong predictor of CV disease and mortality in MHD patients [26]. Previous studies reported both malnutrition and inflammation may affect serum ADMA levels especially in chronic kidney disease patients [27].
Moreover, phase angle (PhA) is a simple non-invasive technique that predicts nutritional status [28]. Gener-

ally, a low PhA shows a disrupted ability of store energy [29]. However, PhA may be affected by fluid status especially in MHD patients. In present study ECW/ICW ratios were similar in two groups thus we could regard as PhA as an indicator for nutritional status. In present study, patients with higher NLR and PLR had higher levels of ADMA and lower levels of PhA had worse nutritional status that demonstares ADMA and PhA may be used as early predictors of nutritional status in MHD patients.

Limitations

The limitations of present study include, firstly, the quite weak statistical power in relation to the small number of patients; secondly, other anthropometric measurements should be added to incease the power of study.

CONCLUSION

In conclusion our study suggests that NLR, PLR and ADMA are independent predictors for nutritional status and inflammation in patients ongoing hemodialysis. Thus, these parameters via complete blood count can be used as an early marker for detecting nutritional status in MHD patients.

Authors' Contribution

Study Conception: BGD; Study Design: BGD; Supervision: MŞK; Funding: BGD; Materials: BGD; Data Collection and/or Processing: BGD; Statistical Analysis and/or Data Interpretation: MŞK; Literature Review: BGD; Manuscript Preparation: BGD and Critical Review: MŞK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The relationship between preoperative hemoglobin, albumin, lymphocyte, and platelet (HALP) score and right colon cancer surgery outcomes: a retrospective cohort study

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ABSTRACT

Objectives: This study aims to investigate the association between the preoperative Hemoglobin Albumin Lymphocyte Platelet (HALP) score and surgical outcomes in right colon cancer patients.
Methods: This retrospective cohort study included patients undergoing elective right colon adenocarcinoma surgery from January 2017 to June 2023 at Bursa Yuksek Ihtisas Training and Research Hospital. The HALP score, calculated from hemoglobin, albumin, lymphocyte, and platelet levels, aimed to predict perioperative morbidity through receiver operating characteristic (ROC) curve analysis.
Results: The study involved 67 patients, mostly male with an average age of 68.28 years, undergoing 46 open and 21 laparoscopic surgeries. Although the HALP score's cutoff value was established, it did not significantly predict perioperative morbidity (P>0.05). However, lower platelet counts (<318×103/L) and open surgery type correlated significantly with higher morbidity (P<0.05).
Conclusions: This study reveals that the HALP score may not effectively predict perioperative morbidity in right colon cancer surgeries, highlighting platelet counts as a more promising marker. Our findings also confirm the increased morbidity associated with open surgeries, challenging existing assumptions and guiding clinical practice.
Keywords: Colon cancer, surgery, morbidity, nutrition

Colon cancer is the second leading cause of mortality from cancer globally and is categorized based on its anatomical site [1-3]. The differentiation of right and left colon cancer is crucial to optimize approaches to therapy, considering their distinct molecular and immunological pathological characteristics [4-6].

While there is growing interest in exploring alternative treatment approaches for colon cancer, it is widely acknowledged that surgery remains the most

efficacious treatment modality. Consequently, accurately predicting and proactively preventing perioperative complications is of crucial significance to ensure optimal outcomes [1, 7].

Malnutrition is a common occurrence among individuals diagnosed with cancer, and it has been linked to the development of various perioperative complications [8, 9]. The Hemoglobin Albumin Lymphocyte Platelet (HALP) score, a metric thought to indicate the immune nutritional status of individuals diagnosed with cancer, has been extensively investigated across various cancer types, including colorectal cancer [10]. The HALP score is determined by the formula: (hemoglobin concentration in grams per liter multiplied by albumin concentration in grams per liter multiplied by lymphocyte count per liter divided by platelet count per liter). These four markers are important factors that should be considered when assessing the immune and nutritional status of cancer patients [11].

The purpose of this study is to investigate the relationship between surgical outcomes in patients diagnosed with right colon cancer and the HALP score, a metric that assesses immune-nutrition status.

METHODS

A retrospective study was conducted on patients who underwent elective surgery for right colon adenocarcinoma at our clinic from January 2017 to June 2023 at Bursa Yuksek Ihtisas Training and Research Hospital. This study was approved by clinical research ethics committee of the Bursa Yuksek Ihtisas Training and Research Hospital (Decision number: 2011-KAEK-25 2023/10-03, Date: 18.10.2023). At our clinic, patients diagnosed with right colon cancer following a colonoscopic examination undergo a comprehensive evaluation by a multidisciplinary tumor council. Subsequently, surgical procedures according to the principles of total mesocolic excision are performed either laparoscopically or by open surgery.

As previously indicated, our study focused specif-
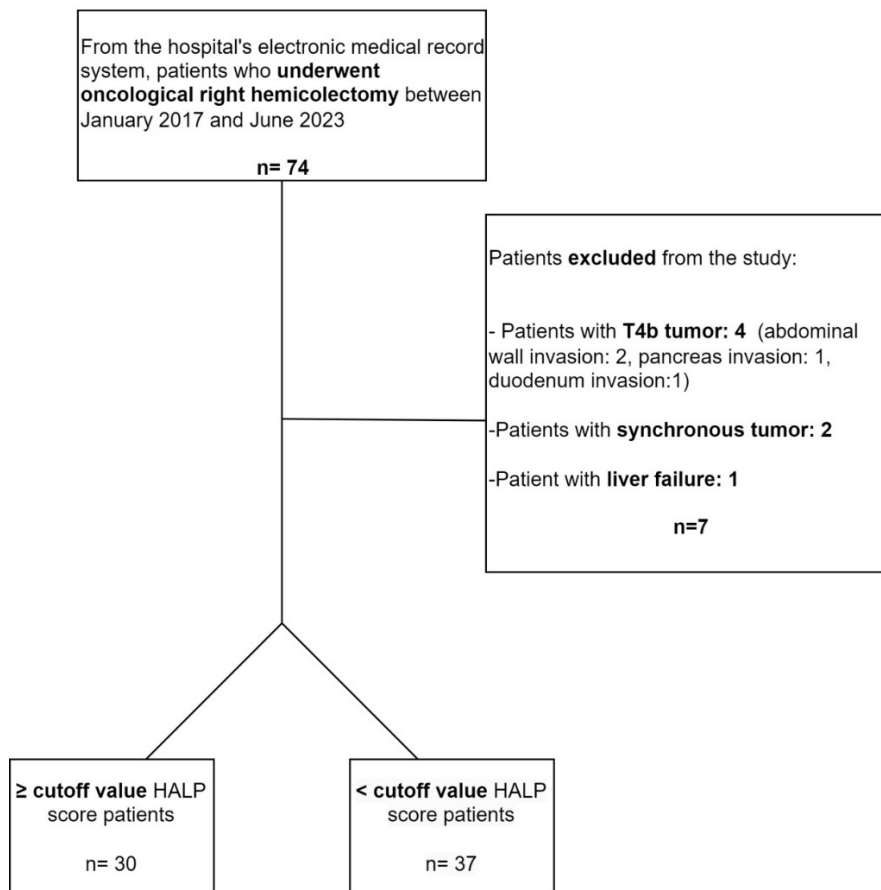
Fig. 1. Flowchart for patient selection and evaluation.

ically on patients with right colon cancer rather than including all individuals with colorectal tumors, due to the notable pathological and clinical distinctions between these subgroups. The hypothesis proposes that patients who exhibit a favorable immunonutrition status, specifically those with elevated HALP scores, are likely to experience improved surgical outcomes. The present study aimed to assess the superiority of surgical outcomes through analyzing the incidence of morbidity during the perioperative period of 30 days. Our assessment for complication was based on the Clavien-Dindo Classification system.

Patiences eligible for this study were adults over the age of 18 who were diagnosed with adenocarcinoma through colonoscopic examination and underwent total mesocolic excision. The study excluded patients presenting with T4b stage adenocarcinoma involving adjacent organs, those with synchronous or metachronous tumors, and those suffering from severe organ failures, such as in the heart or liver (Fig. 1).

Statistical Analysis

Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean ± standard deviation (SD), with minimum and maximum values. For categorical variables, Chi-square or Fisher's exact tests were utilized. The optimal cutoff point for the HALP score in relation to morbidity was defined as the point closest to 0% false positive and 100% true positive on the ROC (Receiver Operating Characteristic) curve. For comparing parameters with normal distribution across HALP groups, Student's t-test was employed, while the Mann-Whitney U test was used for parameters not showing a normal distribution in HALP groups. In the research, initial analyses of age, gender, certain clinical features, and laboratory results on morbidity were conducted using Univariate Logistic Regression (LR). Subsequently, variables found to be significant were analyzed using Stepwise Multivariate LR (Enter method). Quantitative variables were included in the logistic regression model based on their median values as cutoff points. A P-value of <0.05 was considered statistically significant. Clinical data were analyzed using IBM SPSS (IBM Corporation, Armonk, New York, United States) version 25.

Table 1. Sociodemographic and clinical characteristics of the cases (n=67)

Parameters	Data
Gender, n (%)	
Male	35 (52.2)
Female	32 (47.8)
Age (years)	68.28±12.14 (38-89)
BMI (kg/m^2)	28.38±3.73 (20-37.1)
ASA score, n (%)	
1	3 (4.6)
2	32 (47.7)
3	32 (47.7)
Operation type, n (%)	
Open procedure	46 (68.6)
Laparoscopic procedure	21 (31.4)
Length of stay (days)	
Open procedure	9±4.1 (5-25)
Laparoscopic procedure	7±1.8 (4-13)
Overall	9.04±3.67 (4-25)
Surgery duration (min)	
Open procedure	183.10±55.19 (100-300)
Laparoscopic procedure	204.57±50.25 (120-320)
Overall	197.94±52.37 (100-320)
Number of lynph nodes dissected	
Open procedure	21±10.7
Laparoscopic procedure	23±7.7
Tumor size (cm)	5.7±2.5 (2-15) cm
Tumor localization, n (%)	
Cecum	23 (34.3)
Cecum (ileocecal valve)	3 (4.4)
Ascending colon	16 (23.8)
Hepatic flexure	19 (28.3)
Transverse colon proximal	6 (8.9)
T stage, n (%)	
T	2 (2.9)
T2	3 (4.4)
T3	40 (59.7)
T4	22 (32.8)

Table 1 contunied.

TNM stage, n (%)	
1	5 (7.4)
2A	19 (28.3)
2B	10 (14.9)
3A	4 (5.9)
3B	20 (29.8)
3C	9 (13.4)
Lymphovascular invasion, n (%)	
Yes	27 (40.3)
No	40 (59.7)
Hemoglobin (g/dL)	96.85±35.88 (8-147)
Albumin (g/L)	37.46±42,76 (2-371)
Platelets (×10³/L)	322.49±97.74 (105-622)
Lymphocyte(×10³/L)	1.75±0,68 (0.27-3.6)
HAALP score	22.28±14.92 (1-76)
Readmission, n (%)	
Yes	7 (10.6)
No	59 (89.3)
Morbidity, n (%)	
Yes-open procedure	22/46 (47,8)
Yes-laparoscopic	5/21 (23,8)
Clavian-Dindo morbidity score, n (%)	
<3	16 (59.3)
≥3	11 (40.7)
Mortality, n (%)	
Yes	1 (1.5)
No	66 (98.5)

Qualitative variables are presented as n (%), and quantitative variables are presented as mean±standard deviation (min-max). BMI=Body Mass Index, ASA= American Society of Anaesthesiologists, T=Tumor, TNM=Tumor, lmph node, metastasis, BMI=Body Mass Index, ASA=American Society of Anaesthesiologists

RESULTS

The demographic, clinical, and pathological features of 67 patients who underwent surgery are listed in Table 1. The study sample comprised 35 (52.2%) male and 32 (47.8%) female patients. The average age of the cases was 68.28±12.14 years (range: 38-89). The mean BMI was 28.38±3.73 (range: 20-37.1). The average values and standard deviations for HALP score, tumor size, number of lymph nodes, operation and hospitalization durations, were calculated as 22.28±14.92, 5.7±2.5 cm, 23.18±9.78, 197.94±52.37 minutes, 9.04±3.67 days, respectively. Among the cases, 32 (47.7%) had an ASA score of 2, 46 (68.6%) underwent open surgery, and 23 (34.3%) had tumors located in the cecum. Forty patients (59.7%) were in stage T3, twenty (29.8%) in pathological stage 3B, and lymphovascular invasion was observed in 27 (40.3%) cases. Clinically, 7 patients (10.6%) were readmitted, morbidity was observed in 27 (40.3%), and there was 1 case (1.5%) of mortality.

In this study, a ROC (Receiver Operating Characteristic) curve was drawn using the HALP parameter to assess morbidity in cases (Fig. 2). Upon conducting ROC analysis, it was determined that the cutoff point for the HALP value, which could predict patients with morbidity, was values less than 21.5. It was found that the HALP index's ability to distinguish patients with morbidity was not statistically significant (P=0.498). According to this cutoff point, the area under the ROC curve (AUC) was calculated to be 0.549, with a Sensitivity of 55.6% and a Specificity of 62.5% (Table 2). The clinicopathological characteristics of patients in high and low HALP groups were compared in Table 3. Thirty-seven patients were classified into the low HALP group, while thirty were assigned to the high HALP group. Upon examining the results, it was observed that there were no statistically significant differences in the demographic, surgical, and pathological parameters of the cases. Naturally, in laboratory results, Hemoglobin (HB), Platelet (PLT), and Lymphocyte (LYM) values were found to be associated with HALP (P<0.05).

The distribution of surgical characteristics among cases in high and low HALP groups was compared in Table 4. Upon examination of the results, it was found that the distribution of surgical characteristics, other than morbidity, had no association with HALP (P>0.05).

After conducting a Univariate Logistic Regression
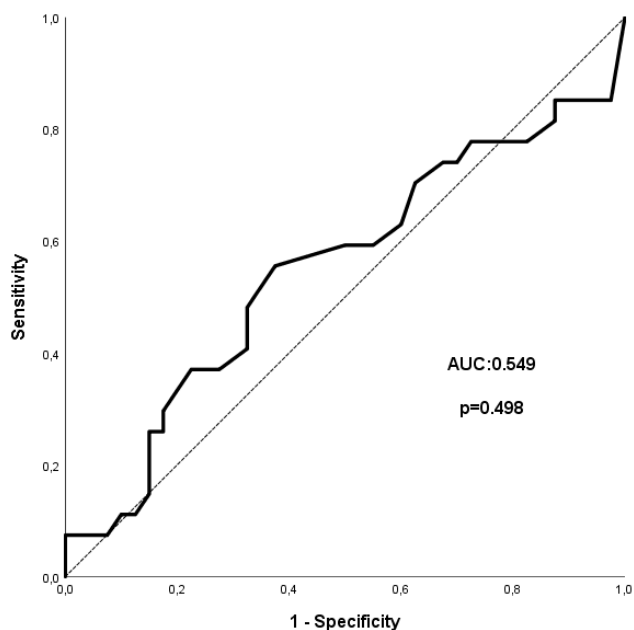
Fig. 2. Receiver operational characteristic (ROC) curve of HALP score to predict morbidity in cases.

(LR) analysis, it was observed that the type of operation, incidence of readmission, and platelet (PLT) variables were statistically significant risk factors for morbidity in Table 5 (P<0.05). It was determined that cases with open surgery had a 3.443 times higher risk of morbidity compared to those with laparoscopic surgery (1.090-10.879) (P=0.035). Similarly, cases with readmission had a 6.158 times higher risk of morbidity compared to others (1.134-33.427) (P=0.035). Additionally, cases with PLT values below 318 000/L had a 4.177 times higher risk of morbidity than those with PLT values above 318 (1.452-11.673) (P=0.008). It was found that the HALP score, based on the determined cutoff value, did not have a significant relationship with perioperative morbidity. Factors found to be significant were included in the Multivariate LR (Multivariate Logistic Regression) model using the Enter method. Upon examination of the results, it was established that the significance of PLT values continued in the Multivariate LR model.

DISCUSSION

Based on the statistical analysis findings obtained from our dataset, it is not possible to establish a significant association between the HALP score and perioperative morbidity in patients with right colon cancer. Based on our findings, it is interesting to consider the higher prevalence of morbidity among patients with platelet values below 318×10^3/L , as indicated in the existing literature [12].

Chaouch et al. [13] 's analysis of the demographic information of the patients included in the study suggests that, in comparison to the literature on right colon cancer surgery series, our patient profile is more geriatric (mean age=68.28 years). Our preponderance of male patients (52%) is consistent with the published data, and it is possible to conclude that our patients are more obese (mean BMI=28.38 kg/m^2) than the patients described in the literature [14-20]. With an ASA score of 3 for 47% of our patients, we are able to claim

Table 2. ROC analysis of the Halp scores of the cases on morbidity

Parameter	Cut-off	AUROC	95 % CI	Sensitivity (%)	Specificity (%)	P
HALP	≤21.5	0.549	0.403-0.696	55.6	62.5	0.498

AUROC: Area Under the ROC, CI: Coenfidence Interval

Table 3. Comparison of distributions of patient characteristics according to HALP score cut-off point

	HALP <21.5 (n=37)	HALP >21.5 (n=30)	P value
Gender, n (%)			
Male	23 (62.2)	12 (40)	0.071*
Female	14 (37.8)	18 (60)	
Age (years)	69.57±12.21 (39-88)	67.5±11.5 (38-89)	0.482‡
BMI (kg/m²)	28.52±3.76 (22-37.1)	28.39±3.71 (20-32.8)	0.887‡
Tumor size (cm)	6±2.4 (2-13)	5.4±2.7 (2.5-15)	0.293‡
Number of lmph nodes dissected	22.27±9.78 (4-52)	24.03±9.92 (7-52)	0.468‡
Hemoglobin (g/dL)	89.84±38.71 (8-134)	105.5±30.47 (10-147)	**0.044†**
Albumin (g/L)	32.19±10.19 (3-46)	43.97±62.88 (2-371)	0.582†
Platelets (×10³/L)	357.19±95.81 (184-622)	279.7±83.16 (105-461)	**0.001‡**
Lymphocyte(×10³/L)	1.48±0.51 (0.27-2.5)	2.08±0.72 (0.68-3.6)	**0.001‡**
ASA Score, n (%)			
1	2 (5.4)	1 (3.3)	0.199*
2	14 (37.8)	18 (60)	
3	21 (56.8)	11 (36.7)	
Type of operation, n (%)			
Open procedure	27 (73)	19 (63.3)	0.395*
Laparoskopic procedure	10 (27)	11 (36.7)	
Tumor lacalization, n (%)			
Cecum	12 (32.4)	11 (36.7)	0.671*
Cecum (ileocecal valve)	2 (5.4)	1 (3.3)	
Ascending colon	9 (24.3)	7 (23.3)	
Hepatic flexure	9 (24.3)	10 (33.3)	
Transverse colon proximal	5 (13.5)	1 (3.3)	
T stage, n (%9			
T1	1 (2.7)	1 (3.3)	0.956*
T2	2 (5.4)	1 (3.3)	
T3	21 (56.8)	19 (63.3)	
T4	13 (35.1)	9 (30)	
TNM stage, n (%)			
1	3 (8.1)	2 (6.7)	0.857*
2A	12 (32.4)	7 (23.3)	
2B	5 (13.5)	5 (16.7)	
3A	2 (5.4)	2 (6.7)	
3B	9 (24.3)	11 (36.7)	
3C	6 (16.2)	3 (10)	
Lymphovascular invasion, n (%)(%)			
None	21 (58.3)	18 (60)	0.861*
Exist	15 (41.7)	12 (40)	

Qualitative variables are presented as n (%), and quantitative variables are presented as mean±standard deviation (min-max). BMI=Body Mass Index, ASA= American Society of Anaesthesiologists, T=Tumor, TNM=Tumor, lmph node, metastasis, *P value was obtained from chi-square test, †P value was obtained from Mann Whitney U test, ‡P value was obtained from Student's t test.

Table 4. Comparison of the distribution of surgical characteristics of the cases according to the HALP score cut-off point

	HALP <21.5 (n=37)	HALP >21.5 (n=30)	P value
Surgery duration (min)			
Open procedure	197.04±51.84 (120-315)	209.21±41.51 (140-300)	0.400†
Laparoscopic procedure	179.50±44.75 (120-255)	186.36±65.31 (100-300)	0.784†
Length of stay (day)	8.62±50.04 (5-20)	9.60±4.48 (4-25)	0.510†
Tumor size (cm)	6.01±2.42 (2-13)	5.35±2.67 (2.5-15)	0.114†
Number of lymph nodes dissected	22.27±9.78 (4-52)	24.03±9.92 (7-52)	0.384†
Readmission, n (%)			
Exist	4 (10.8)	3 (10.3)	0.921*
None	33 (89.1)	26 (89.7)	
Mortality, n (%)			
Exist	0 (0)	1 (3.3)	0.448*
None	37 (100)	29 (96.7)	

Qualitative variables are presented as n (%), and quantitative variables are presented as mean±standard deviation (min-max). *P value was obtained from chi-square test, †P value was obtained from Mann Whitney U test

Table 5. Univariate and multivariate logistic regression analysis of clinical and surgical characteristics of the cases based on morbidity

	Univariate LR OR (95% CI)	P value	Multivariate LR OR (95% CI)	P value
Gender (ref: male)	1.190 (0.449-3.150)	0.726		
Age>70 (ref≤70)	2.273 (0.843-6.126)	0.105		
BMI >30 (ref≤30)	0.277 (0.031-2.513)	0.254		
ASA score 3 (ref≤2)	2.273 (0.843-6.126)	0.105		
Type of procedure - Open(ref: Lap)	3.443 (1.090-10.879)	0.035		
Tumor size >5 (ref≤5 cm)	0.971 (0.362-2.606)	0.953		
Number of dissecten lymph node >22 (ref≤22)	0.884 (0.335-2.338)	0.804		
T stage >2 (ref≤2)	12.125 (0.015-45.151)	0.999		
TNM stage=3 (ref≤2)	1.636 (0.425-6.301)	0.474		
Lymphovascular invasion	1.724 (0.637-4.669)	0.284		
Operation duration >190 (ref≤190)	0.691 (0.260-1.834)	0.458		
Readmission	6.158 (1.134-33.427)	0.035		
Hemoglonin>106 (ref≤106)	0.691 (0.260-1.834)	0.458		
Albumin>35 (ref≤35)	0.639 (0.233-1.755)	0.385		
Platelets≤318 (ref>318)	4.117 (1.452-11.673)	**0.008**	4.501 (1.077-18.801)	**0.04**
Lymphocyte>1.7 (ref≤1.7)	0.567 (0.212-1.511)	0.256		
HALP <21.5	2.083 (0.772-5.623)	0.147		

LR=Logistic regression, CI=Confidence interval, Lap=Laparoscopic

that they are more comorbid than those reported in the literature, with the exception of the series by Chen et al. [21].

Our operation times for laparoscopic right hemicolectomy are consistent with current surgical standards, averaging 204.57 minutes, which is consistent with the 201.31 minutes reported by Zedan et al. [22]. However, our open surgeries averaged 183.10 minutes, exceeding the durations reported by Zedan et al. [22] at 152.04 minutes, Chen et al. [21] at 123/118.5 minutes, and Han et al. [17] at 110/133 minutes. These extended times in open procedures could reflect the complexities involved in managing a geriatric and comorbid patient cohort. At this point, our oncological laparoscopic right hemicolectomy performance is comparable to that of the literature; however, our oncological open right hemicolectomy operation time lags behind that of the literature.

In terms of hospital stays, our study shows shorter durations, ranging from 7.18 to 9.41 days, compared to the values reported by Zedan et al. [22] (9.13 to 13.04 days), Chen et al. [21] (9.2 to 15.2 days), and Li et al. [23] (18.5 to 17 days). The reduced length of hospital stays, particularly in open surgeries, may highlight the efficiency of our postoperative care protocols and indicate areas for potential improvement in patient management and discharge processes.

The number of lymph nodes retrieved in our surgeries, ranging from 21 to 23, meets the recommended threshold for accurate staging, which is above the 12-node minimum noted in the literature [22]. This node count is consistent with findings from Sheng et al. [20] who reported 19.2 to 19.9 nodes but is lower than the counts in studies by Zedan et al. [22] at 32.65 to 39.8 and Chen et al. [21] at 24.8 to 22.4. Our approach to lymph node dissection remains robust and ensures comprehensive staging essential for guiding treatment decisions.

Our perioperative morbidity rates for open oncological right hemicolectomy are 22/46 (47.8%) and for laparoscopic oncological right hemicolectomy to be 5/21 (23.8%), respectively, in comparison to the literature rates of 36.3% to 23.2% [14], 21.3% to 18.3% [19], and 27.2% to 14.7% [22]. While there is no clear advantage of laparoscopic or open surgery over the other in terms of perioperative morbidity [13], our morbidity rates, particularly in open surgery, are higher than those reported in the literature. The anas-

tomotic leak was categorized according to the Clavien-Dindo classification system as grade 3b. The occurrence rate of this complication was observed to be 2 out of 46 (%4,3) cases in open surgery and 1 out of 21 cases (4.7%) in laparoscopic surgery. One patient required a second surgical intervention as a result of evisceration, while another patient necessitated reoperation due to post-operative bleeding. The cause of our mortality was caused by sepsis that occurred because of anastomotic leakage.

The current research explores the association between HALP score and colorectal cancer, primarily focusing on overall survival and disease-free survival outcomes [10, 24, 25]. Research studies have demonstrated that when the HALP score above a specific threshold, there is a correlation with improved survival outcomes [24-26]. In our study, we endeavored to examine the correlation between the HALP score and perioperative morbidity in the context of right colon surgery. In the colorectal surgery study conducted by Yalav et al. [25], it was observed that there was no significant association between perioperative morbidity and the HALP score.

The composition of the tumor microenvironment depends on by the presence of inflammatory cells and host cells, and it has been suggested that it has a critical role in determining the clinical outcome [27]. Currently, there existed studies indicating that the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, albumin, and hemoglobin, when examined in peripheral blood, demonstrate association with the prognosis of colon cancer, similar to various other types of cancer [12, 28, 29]. Nevertheless, these factors do not provide conclusive evidence regarding the prognosis [27]. The primary focus of these research focuses around an indicator of overall survival, with no specific threshold established for platelet levels. Furthermore, based on the findings of these studies, there exists a mathematical correlation between elevated platelet levels and a poor outcome in relation to overall survival. Hence, it is obvious that no comparable findings exist in the current pool of literature regarding the association between perioperative morbidity and the additional outcome of our study, specifically the presence of 318,000 platelets.

Limitations

There are certain limitations inherent in our study

that need to be acknowledged. Firstly, the retrospective nature of our study raises concerns regarding the generalizability of our findings. Additionally, the limited number of patients included in our study further restricts the applicability of our results, particularly within a relatively specific group. Enhanced outcomes can be achieved for this subject matter through the utilization of larger sample sizes. In essence, while our study contributes valuable insights into the realm of right colon cancer surgery, it also highlights the need for continual, expansive research to unravel the intricate interplay of various factors influencing patient outcomes.

CONCLUSION

Our study highlights demographic features such as a geriatric population and higher BMI, which may influence morbidity outcomes in right colon cancer surgeries. Despite longer operation times and hospital stays compared to existing reports, our lymph node dissection adhered to standard protocols for accurate staging. Significantly, we found no correlation between the HALP score and perioperative morbidity, challenging previous assertions of its predictive value for survival outcomes in colorectal cancer. Contrary to earlier studies, our data also suggest that elevated platelet levels do not correlate with a better prognosis, calling for a reevaluation of their prognostic significance.

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Obstructions of prosthetic heart valves: diagnosis and treatment considerations

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ABSTRACT

Objectives: Since the first years of native heart valve replacement by - prosthetic valves; prosthesis thrombogenicity has kept its importance as a serious problem causing post-operative morbidities and mortality. This study aims to evaluate early postoperative morbidity and mortality of patients diagnosed with prosthetic valve thrombosis and treated surgically or non-surgically.

Methods: Thirty-one patients diagnosed with and treated for prosthetic valve thrombosis were evaluated retrospectively. The patients were followed up for 58 months.

Results: There were 24 females and 7 males. The mean patient age at the time of prosthetic valve thrombosis diagnosis was 40.7±11(range, 10-57) years. The mean duration between prosthetic valve replacement and the first signs of prosthetic valve thrombosis was 67. 67±66 (range, 1to 300) months. All patients presented with a functional capacity of NYHA Class III or IV. A total of 32 interventions; 27 surgical and 5 thrombolytic treatments due to elevated aortic prosthetic valve pressure gradient which did not improve with thrombolysis. Of 27 surgical interventions for thrombosed prosthetic valves, 21 involved mitral, 2 aortic, and 4 tricuspid positions. A total of 9 patients died during follow-up. The overall mortality rate was 29.03%. The mortality rate was 29.62 % after surgical interventions and 20% after thrombolytic treatment.

Conclusion: Currently prosthetic valve replacement is the basic palliation method in the management of patients with diseased native heart valves. In the majority of mechanical prosthetic valve obstructions, the main pathology is fibrous tissue proliferation-related to irregular warfarin usage, which in turn causes the development of acute symptoms secondary to acute valve thrombosis. The necessary treatment method for prosthetic valve obstructions should be either the use of thrombolytic agents or the replacement of the obstructed prosthetic valve with a new one.

Keywords: Obstructions, prosthetic heart valves, treatment

Since the first years of native heart valves' replacement by - prosthetic valves; prosthesis thrombogenicity has kept its importance as a serious problem causing post-operative morbidities and mortality. To eliminate the ball-cage valve and disc-cage valves' non-physiologic transprosthetic flow profiles; tilting-disc and bi-leaflet prosthetic valves have been developed [1]. However, bi-leaflet valves have

surpassed other valve technologies and become the standard design with their anti-thrombogenic properties, flow dynamics close to physiological flow, easy implantability, and minimal contact with the subvalvular apparatus [2]. To reduce the thrombogenicity of the prosthetic materials to a minimum, the leaflets of the valves are manufactured with pyrolytic carbon. Besides the structural integrity of its own, pyrolytic carbon develops a biological adaptation to the living body by having a protein coating on its surface [3, 4, 5].

Prosthetic valve thrombosis has been described as occlusion of the prosthetic valve by a non-infective thrombotic material [6]. Prosthetic valve dysfunction because of valve size mismatch, infective vegetations, and restriction of the leaflet's moving parts by surgical suture materials are beyond this description. The risk of developing prosthetic valve thrombosis varies depending on the type of valve used, the position of the valve implanted, and the side of the heart. The risk of thrombosis is higher in mechanical valves compared to biological valves, in those implanted in the mitral position compared to those in the aortic position, and in prosthetic valves on the right side of the heart compared to those on the left side. This result develops with the interaction of the patient-related (coagulability, cardiac function, and cardiac morphology) and prosthesis-related multiple factors [7].

With this study, we aimed to report the findings and results of our patients diagnosed and treated with prosthetic valve thrombosis by comprehensively comparing them with the literature.

METHODS

This retrospective clinical study was performed at Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital. All patients admitted to the cardiac surgery center with Prosthetic Valve Obstruction were included in this study.

Thirty-one patients diagnosed with and treated for prosthetic valve thrombosis were retrospectively evaluated in a single center (24 females, 7 males). The patients were followed up for 58 months. When a prosthetic valve thrombosis diagnosis has been made.

An echocardiographic exam was also performed for every patient included in this study. Echocardiographic parameters including prosthetic valve gradients and functional status examined (Fig. 1). Pulmonary arterial and Pulmonary Capillary Wedge Pressures with the Central Venous Pressure recorded after Swan-Ganz Catheter insertion.

All patients presented with a functional capacity of New York Heart Association (NYHA) Class III or IV. Thrombolytic agents used to treat prosthetic valve thrombosis were Streptokinase (Kabikinase® Pharma-
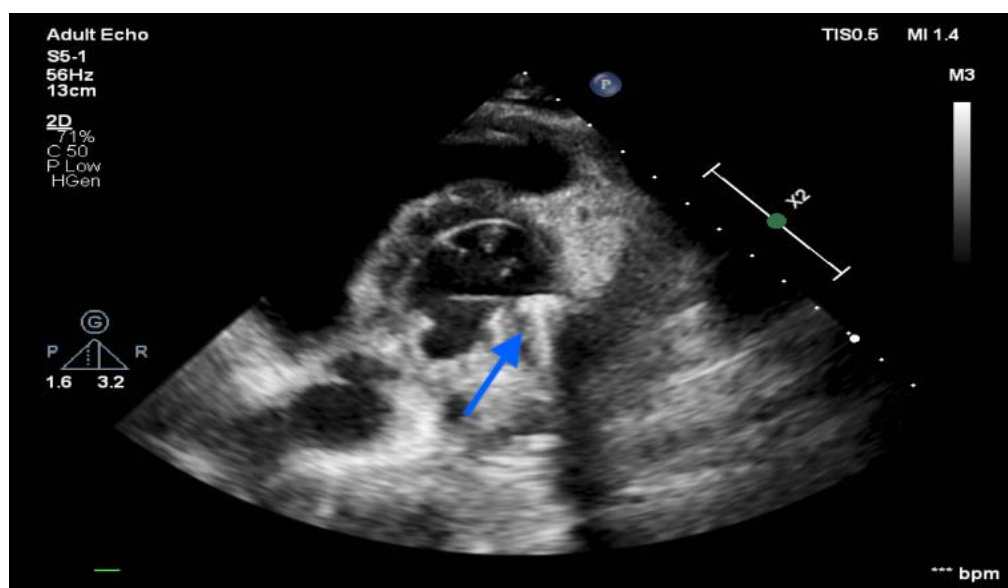

Fig. 1. Preoperative echocardiogram image demonstrating prosthetic valve thrombosis (blue arrow).

cia & Upjohn Sweden) and recombinant plasminogen activator (Actilyse®, Boehringer Ingelheim GmbH Germany).

The total dose of Streptokinase was 1. 500000 IU Per case with 250. 000 IU infused over 20 minutes and the rest of the total dose infused over 90 min. A total dose of recombinant plasminogen activator was 100 mg per case, with 10 mg infused in 2 minutes, an additional 40 mg infused in the first 1 hour, and the rest of the total dose infused in the first 2 hours.

All patients treated with thrombolytic agents received 25. 000 IU of unfractionated heparin in the first 24 hours of the treatment titrated by thromboplastin times kept at 2 times above the normal range (Table 1).

Statistical Analysis

Descriptive statistics were reported, including counts (n), percentages (%), mean±standard deviations, and median (minimum and maximum) values.

RESULTS

A total of 32 interventions; 27 surgical and 5 thrombolytic therapy, were performed on 31 patients. The mean patient age at the time of prosthetic valve thrombosis diagnosis was 40.7±11 (range, 10-57) years. The mean duration between prosthetic valve replacement and the first signs of prosthetic valve thrombosis was 67.67±66 (range, 1-300) months.

Patients had a mean left atrial diameter of 6.13±1.4 cm (range, 4. 3 to 10) by echocardiographic evaluation. Hemodynamic parameters of patients by Swan-Ganz catheter measurement were as follows; pulmonary capillary wedge pressure (PCWP): 26±8.3 mmHg, systolic pulmonary artery pressure (PAP systolic): 54±16 mmHg (range, 31 to 80), and diastolic pulmonary artery pressure (PAP diastolic): 27±10 mmHg (range, 13 to 48).

Of 31 patients, 26 had undergone single valve replacement, and 5 had undergone double valve replacement procedures during their initial heart valve operations. The transvalvular diastolic pressure gradient in patients with prosthetic mitral valve dysfunction was 19±9 mmHg (range, 8 to 45). In two patients with aortic prosthetic valve dysfunction transvalvular systolic pressure gradient was 77 and 88 mmHg. In four

patients with prosthetic tricuspid valve dysfunction mean transvalvular diastolic pressure gradient was 13. 8 mmHg (range, 9 to 16) (Table 1).

One patient underwent surgery following thrombolytic treatment due to elevated aortic prosthetic valve pressure gradient which did not improve with thrombolysis. Of 27 surgical interventions for thrombosed prosthetic valves, 21 involved mitral, 2 aortic, and 4 tricuspid positions.

Mitral valve interventions included replacement of the dysfunctional prosthetic valve and thrombectomy and debridement of the malfunctional prosthesis in 17 patients. One patient with a dysfunctional prosthetic mitral valve died during the redo-sternotomy opening.

Primary aortic valve replacement was performed due to de novo native aortic valve disease during surgical management of prosthetic mitral valve dysfunction in 3 patients with prosthetic mitral valve thrombosis. In the same group, tricuspid valvular interventions were performed for concomitant tricuspid pathologies in five patients. Four of the tricuspid interventions were replacement of the native tricuspid valve and one was De Vega annuloplasty.

Of five patients diagnosed with prosthetic tricuspid valve dysfunction, four underwent surgical and one underwent thrombolytic treatment. Prosthetic valve re-replacement was performed on all patients who were surgically treated for tricuspid prosthetic valve dysfunction.

According to surgical explorative findings and pathologic examinations of dysfunctional prosthetic valves explanted from 27 patients who were surgically treated; the findings were pannus and thrombus in 16 cases, fresh thrombus in 7 cases, and biologic valve degeneration in 4 cases (Fig. 2).

Of five patients treated by a thrombolytic agent, thrombosed prosthetic valves were in mitral position in 3 patients, aortic position in one patient, and tricuspid position in one patient.

Seven patients died during the first 24 h. after interventions. 6 following surgical treatment and one following thrombolytic treatment. Surgically treated seven patients died in the early postoperative period.

Causes of mortality were peri-operative low cardiac output syndrome and; failure to wean from cardiopulmonary bypass for six patients and sepsis and

Table 1. Patients demographic data, findings, and treatment options

Number	Age	Gender	Time	Prosthetic valve type	Clinical Picture	NYHA class	Anticoagulation regimen	Rhythm	Pre-Op Echocardiography
1	46	F	1 month	MVR (29) – Carbomedics mechanical prosthetic valve	Pulmonary edema	IV	Irregular/ Insufficient	AF	Restricted leaflet movements in Prosthetic valve + Tricuspid stenosis
2	42	F	7 months	MVR (27) – Carbomedics mechanical prosthetic valve	Respiratory distress	III	Irregular/ Insufficient	NSR	Left atrial thrombus
3	43	M	24 months	MVR (31) – Sorin mechanical prosthetic valve	Pulmonary edema	IV	Irregular/ Insufficient	AF	Complete prosthetic valve Thrombosis+ 2 cm in diameter echo-dens thrombus above the valve
4	46	F	23 months	MVR (27) – Medtronic mechanical prosthetic valve+ Left atrial thrombectomy	Pulmonary edema	IV	Irregular/ Insufficient	AF	Restricted leaflet movements+Left atrial thrombus
5	30	M	30 months	MVR (27) - St.Jude mechanical prosthetic valve + Aortic valvotomy	Congestive heart failure	III	Irregular/ Insufficient	AF	Restricted leaflet movements+ Aortic regurgitation
6	39	F	9 months	MVR (29) – Carbomedics mechanical prosthetic valve	Pulmonary edema	IV	Irregular/ Insufficient	AF	Restricted leaflet movements
7	48	M	28 months	MVR (29) – Carbomedics mechanical prosthetic valve	Pulmonary edema	IV	Irregular/ Insufficient	AF	Restricted leaflet movements
8	52	F	20 months	MVR (29) – Sorin mechanical prosthetic valve + CABGx1	Pulmonary edema	IV	Irregular/ Insufficient	AF	Disc movements severely restricted
9	34	F	26 months	MVR (27) – Carbomedics mechanical prosthetic valve	Respiratory distress	III	Irregular/ Insufficient	AF	Restricted leaflet movements
10	38	F	8 months	MVR (29) – Carbomedics mechanical prosthetic valve	Respiratory distress	III	Regular/ Sufficient	AF	leaflet movements limited on anterior leaflet in the prosthetic valve, posterior leaflet is normal
11	48	F	42 months	MVR (29)+TVR (31) – Sorin mechanical prosthetic valves	Congestive heart failure	IV	Irregular/ Insufficient	AF	Disc movements severely restricted on the Tricuspid prosthetic valve
12	52	F	48 months	MVR (29) – Sorin mechanical prosthetic valve + TVR (31) Hancock Bioprosthetic valve	Congestive heart failure	III	Irregular/ Insufficient	AF	Restricted leaflet movements in Bioprosthetic Tricuspid valve
13	39	F	102 months	MVR (29) – Hall-Kaster mechanical prosthetic valve	Respiratory distress	III	Regular/ Sufficient	AF	Disc movements severely restricted
14	38	M	180 months	Starr-Edwards (Cage-Ball) mechanical prosthetic valve	Congestive heart failure	III	Regular/ Sufficient	AF	Stenotic prosthetic valve
15	53	F	300 months	Starr-Edwards (Cage-Ball) mechanical prosthetic valve	Congestive heart failure	III	Irregular/ Insufficient	AF	Stenotic prosthetic valve
16	48	F	60 months	MVR (31) – Omniscience mechanical prosthetic valve	Congestive heart failure	III	Irregular/ Insufficient	AF	Disc movements are severely restricted

Table 1. Continued.

Number	Age	Gender	Time	Prosthetic valve Type	Clinical picture	NYHA class	Anticoagulation regiment	Rythm	Pre-Op Echocardiography
17	32	F	12 months	MVR (27) – Carbomedics mechanical prosthetic valve	Pulmonary edema	IV	Irregular/ Insufficient	AF	Restricted leaflet movements
18	34	F	96 months	AVR (19) – Medtronic mechanical prosthetic valve	Chest pain at rest + ST changes on ECG	III	Irregular/ Insufficient	NSR	75 mmHg max gradient on mechanical prosthetic valve
19	34	F	96 months	AVR (19) – Medtronic mechanical prosthetic valve	Chest pain on exertion	II / III	Regular/ Sufficient	NSR	65 mmHg max gradient on mechanical prosthetic valve
20	47	M	42 months	MVR (29) – Sorin mechanical prosthetic valve + CABGx1	Shortness of breath	III	Irregular	NSR	thrombus image on leaflets
21	53	M	42 months	MVR (31) Carbomedics mechanical prosthetic valve	Shortness of breath	III	None	AF	thrombus image on leaflets
22	25	F	42 months	MVR (31) – St.Jude mechanical prosthetic valve	Pulmonary edema	IV	Irregular/ Insufficient	AF	Severely restricted leaflet movements
23	57	F	140 months	MVR (31) – Ionescu-Shiley mechanical prosthetic valve	Congestive heart failure	III	None	AF	Disc movements severely restricted in prosthetic mitral valve + Aortic Stenosis
24	46	F	125 months	MVR (29) + TVR (29) – Björk-Shiley mechanical prosthetic valve + Biocor Bioprosthetic valve	Congestive heart failure	III / IV	Irregular/ Insufficient	AF	Restricted leaflet movements in prosthetic Tricuspid valve
25	42	F	45 months	MVR (27) + TVR (27) – Carbomedics mechanical prosthetic valve + Biocor Bioprosthetic valve	Congestive heart failure	III / IV	Irregular/ Insufficient	AF	Restricted leaflet movements in prosthetic Tricuspid valve
26	54	F	54 months	MVR (31) – Carbomedics mechanical prosthetic valve	Shortness of breath	III	Regular/ Sufficient	AF	Paravalvular leakage +restricted leaflet movements
27	33	F	108 months	MVR (29) – Björk-Shiley mechanical prosthetic valve	Shortness of breath	III	Irregular/ Insufficient	AF	Restricted leaflet movements
28	38	F	204 months	AVR (27) – Carbomedics mechanical prosthetic valve	Chest pain + ST changes on ECG	III / IV	Irregular/ Insufficient	AF	Restricted leaflet movements
29	29	F	62 months	MVR (29) – Carbomedics mechanical prosthetic valve	Pulmonary edema	IV	Irregular/ Insufficient	AF	Restricted leaflet movements
30	21	F	60 months	MVR (31) + TVR (33) – Biocor Bioprosthetic valves	Congestive heart failure	III / IV	Irregular/ Insufficient	AF	Stenotic prosthetic tricuspid valve
31	10	M	48 months	MVR (25) –Biocor Bioprosthetic valve	Congestive heart failure	III / IV	None	NSR	Stenotic prosthetic mitral valve + Aortic regurgitation
32	31	F	110 months	MVR (27) – Biocor Bioprosthetic valve	Congestive heart failure	III / IV	None	AF	Stenotic prosthetic mitral valve

AF=Atrial fibrillation, CABG=Coronary artery bypass graft, ECG=Electrocardiography, AVR=Aortic valve replacement, MVR=Mitral valve replacement, TVR=Tricuspid valve replacement, NSR=Normal sinus rhythm
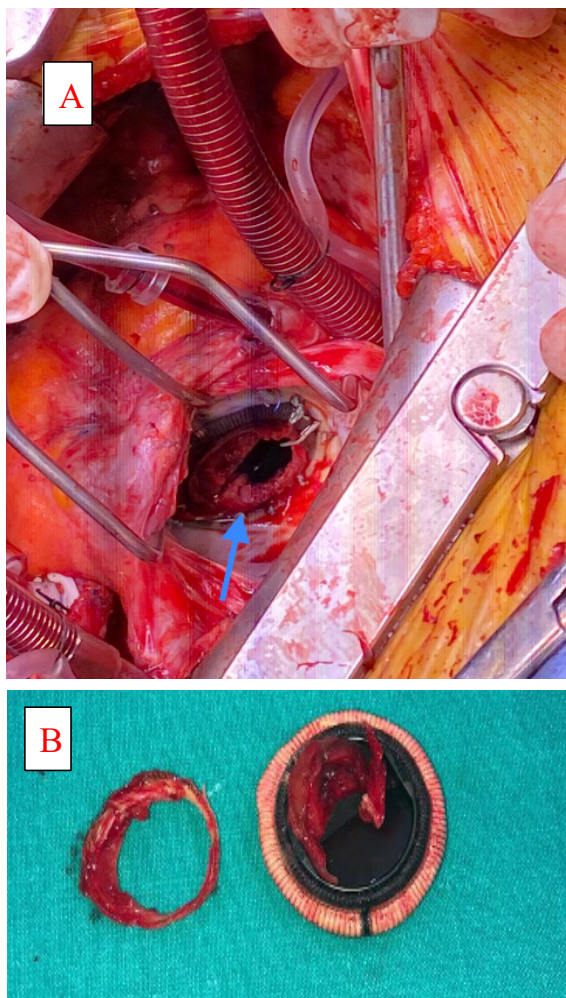
Fig. 2. (A) Intraoperative view of mechanical mitral valve thrombosis(arrow). (B) Mechanical mitral valve thrombosis and pannus.

multiorgan failure for two patients. A total of nine patients died during interventions or within the early postoperative period. Overall mortality was 29.0%, 29. 6% for the surgically treated group and 20. 0% for patients treated by thrombolytic therapy (Table 2).

DISCUSSION

The most frequent indication for prosthetic valve re-operations is prosthetic valve obstruction. Many researchers have reported that prosthetic valve obstruction develops as a consequence of many complex pathological mechanisms. The main component of these mechanisms is fibrous tissue proliferation associated with prosthesis thrombosis which disrupts

normal prosthetic valve function [7, 8].

Fibrous tissue proliferation is responsible for prosthetic valve thrombosis in 80% of cases reported in the medical literature [9, 10]. The leading cause of tissue proliferation is still unknown. However, it has been argued that biocompatibility of the prosthetic valve material, endothelial damage which develops during surgical intervention, post-surgical low cardiac output, trans-prosthetic pressure gradients (especially at mitral position), pregnancy after valve implantation, prosthetic valve endocarditis and insufficient anticoagulant usage; all individually or interacting with each other trigger fibroblast proliferation [11-13].

Pannus formation was diagnosed in 59% of our surgically treated patients, including bioprosthetic valve obstructions. Thrombolytic treatment or simple debridement of the pannus tissue is still far from solving the underlying pathology. We treated aortic prosthetic valve obstruction in a patient by infusing a thrombolytic agent which failed to improve elevated trans-prosthetic valvular pressure gradients. The patient underwent, surgical intervention and debridement of the pannus formation. But surgical debridement would otherwise be unsuccessful or even potentially could cause harm because of the technical difficulty of removing pannus from both sides of the thrombosed prosthetic valve. Fresh thrombus (- primary prosthetic valve thrombosis) is the pathological diagnosis of 20% of surgically treated prosthetic valve obstruction cases in the literature. It was 26% in our series. Thrombosis mainly develops because of prosthetic valve thrombogenicity and ineffective anticoagulant usage [14, 15]. Thrombolytic agent usage or surgical thrombectomy are the available treatment options depending on the clinical condition [16].

In our series debridement and thrombectomy were applied in 3 of our surgically treated patients and re-replacement of the thrombosed prosthetic valve was the treatment of choice in of the cases. Prosthetic valve obstruction diagnosis depends on findings in physical examination, and fluoroscopic, echocardiographic, and hemodynamic studies. The nature of the prosthetic valve obstruction can be further assessed by trans-esophageal echocardiography in detail. Transthoracic echocardiographic evaluation was the main diagnostic tool in our study.

Preserved leaflet or disc movement and echocardiographic images of thrombus are the echocardio-

Table 2. Type of intervention and results

Number	Age	Gender	Per-Op findings	Type of intervention	Results
1	46	F	Fresh thrombus in prosthetic valve orifice	MVR (31) + TVR (31) – Biocor Bioprosthetic valves	Low Cardiac out put+Per operative Exitus
2	42	F	Fresh thrombi in prosthetic valve orifice and left atrium	MVR (29) – St.Jude mechanical prosthetic valve + De Vega Ann.	Exitus at post-op day 17th.
3	43	M	Fresh thrombi in prosthetic valve orifice and left atrium	MVR (27) – Medtronic mechanical prosthetic valve + De Vega Ann.	Low Cardiac out put+Per operative Exitus
4	46	F	Pannus formation + fresh thrombus in the disc slot	MVR (27) – Medtronic mechanical prosthetic valve	Low Cardiac out put+Per operative Exitus
5	30	M	Pannus formation + thrombus in leaflet hinges	AVR (23) + MVR (29) – St.Jude mechanical prosthetic valves	Low Cardiac out put+Per operative Exitus
6	39	F	Fresh thrombi in valve leaflet hinges and left atrium	MVR (27) – St.Jude mechanical prosthetic valve	Complete recovery
7	48	M	Pannus formation + paravalvular leakage	MVR (27) – Carbomedics mechanical prosthetic valve	Exitus at post-op 2nd day (Cerebral edema)
8	52	F	Left atrial thrombus+ Complete obstruction above and below the valve (Thrombus + pannus formation)		Exitus during sternotomy
9	34	F	Pannus formation + fresh thrombus on leaflet hinges	MVR (31) – Hancock Bioprosthetic valve	Complete recovery
10	38	F	fresh thrombus on the anterior leaflet	Thrombectomy + Debridman	Complete recovery
11	48	F	Fresh thrombus in tricuspid prosthetic valve	TVR (31) – Hancock Bioprosthetic valve	Complete recovery
12	52	F	Thrombolytic treatment (r-tPA)		Complete recovery
13	39	F	Pannus formation + fresh thrombus in the disc slot	MVR (27) – Carbomedics mechanical prosthetic valve	Complete recovery
14	38	M	Pannus formation + thrombi in ball socket and cage	MVR (25) – St.Jude mechanical prosthetic valve	Complete recovery
15	53	F	Pannus formation + thrombi in ball socket and cage	MVR (31) – Carbomedics mechanical prosthetic valve + De Vega Ann.	Complete recovery
16	48	F	Pannus formation + fresh thrombus in the disc slot	MVR (29) – St.Jude mechanical prosthetic valve	Complete recovery

Table 2. *Continued.*

Number	Age	Gender	Per-Op findings	Type of intervention	Results
17	32	F		Thrombolytic treatment (Streptokinase)	Exitus at 4th hour, (cerebral embolism)
18	34	F		Thrombolytic treatment (r-tPA)	Regressed symptoms
19	34	F	Pannus formation + fresh thrombus in the disc slot	Debridement + Aortoplasty	Complete recovery
20	47	M		Thrombolytic treatment (Streptokinase)	Complete recovery
21	53	M		Thrombolytic treatment (Streptokinase)	Complete recovery
22	25	F	fresh thrombus on leaflet hinges	MVR (29) – St.Jude mechanical prosthetic valve	Exitus at post-op day 24th (Sepsis)
23	57	F	Bioprosthetic valve degeneration + fresh thrombus on the valve	AVR (21) + MVR (29) – St.Jude mechanical prosthetic valves	Complete recovery
24	46	F	Bioprosthetic valve degeneration and fresh thrombus on tricuspid bioprosthetic valve	TVR (27) – St.Jude mechanical prosthetic valve	Complete recovery
25	42	F	Bioprosthetic valve degeneration + fresh thrombus on the valve	TVR (29) – Biocor Bioprosthetic valve	Complete recovery
26	54	F	fresh thrombus on leaflet hinges+ paravalvular separation from valve annulus+ left atrial thrombus	Paravalvular leakage repair + thrombectomy	Complete recovery
27	33	F	Pannus formation + thrombus in disc slot	MVR (29) -St.Jude mechanical prosthetic valve + De Vega Ann.	Complete recovery
28	38	F	Fresh thrombi on the leaflet hinges	AVR (25) – St.Jude mechanical prosthetic valve	Complete recovery
29	29	F	Fresh thrombi on the leaflet hinges	MVR (27) – Carbomedicsmechanical prosthetic valve	Complete recovery
30	21	F	Bioprosthetic valve degeneration + fresh thrombus on the valve	TVR (31) – Medtronic mechanical prosthetic valve	Complete recovery
31	10	M	Bioprosthetic valve degeneration and calcification + fresh thrombus on the valve	AVR (20) + MVR (25) – Carbomedics mechanical prosthetic valves	Complete recovery
32	31	F	Bioprosthetic valve degeneration + fresh thrombus on the valve	MVR (27) – Medtronicmechanical prosthetic valve+De Vega Ann.	Complete recovery

AVR=Aortic valve replacement, MVR=Mitral valve replacement, TVR=Tricuspid valve replacement

graphic findings in primary prosthetic valve thrombosis besides prosthetic valve hemodynamic parameters such as trans-valvular pressure gradients. Observation of rapid clinical deterioration combined with echocardiographic findings renders primary prosthetic valve thrombosis the most probable diagnosis. Thrombolytic treatment would be the first option in the treatment of this fatal clinical condition in selected cases.

Thrombus images in echocardiographic studies were observed in patients who received thrombolytic treatment in our series (Fig. 1). One of those five patients died in the 4th hour of thrombolytic treatment because of cerebral thrombotic embolization. Risk of the cerebral embolization during thrombolytic treatment of left-sided prosthetic valve thrombosis was reported by several authors [15-20].

In the case of fibrous tissue proliferative invasion of the prosthetic valve orifices preventing leaflet or disc movement; fresh thrombosis is the final phase of the pathological process causing rapid clinical deterioration. In all surgically treated patients in our series, restriction of the leaflet or disc movement was the main echocardiographic finding and was confirmed by pannus determination in prosthetic valve orifices.

Treatment of prosthetic valve obstructions is a serious clinical entity with very high mortality rates approaching 44% [21-27].

The in-hospital mortality rate was 29.9% in our study. This result reflects the seriousness of the clinical symptoms of patients at hospital admission. Six patients admitted with pulmonary edema underwent surgical intervention and five of them died intraoperatively. But early intervention is very important and the overall in-hospital mortality rate shows its importance in our series. In all but four patients, anticoagulation titration was suboptimal. This is a result of inefficient cooperation between patients and healthcare providers.

Limitations

The most important limiting point of the study is the small number of patients. Multicenter studies are needed.

CONCLUSION

We present our clinical experience with a review of

the available literature. Currently, prosthetic valve replacement is the basic palliation method in the management of patients with diseased native heart valves. Prosthetic valves carry an annual thrombosis risk of 0.03 to 4.3% under optimal conditions. Patient compliance with the anticoagulation regimen and its follow-up is our main problem. Echocardiographic evaluation and early detection of hemodynamic abnormalities, and fibrous tissue proliferation (pannus) during routine follow-ups are the key factors in the prevention of secondary prosthetic valve thrombosis. Transesophageal echocardiography is very important in differential diagnosis. In most cases, fibrous tissue proliferation is the main pathological process in the development of mechanical prosthetic heart valve obstructions. In this case replacement of the obstructed prosthetic valve with a new one is the only option in the treatment.

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Exploring menopausal dynamics: a cross-sectional analysis of age, symptomatology, and sociodemographic influences in a developing population of women aged 40-60

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ABSTRACT

Objectives: Menopause, a biological milestone, marks a pivotal phase in women's lives characterized by ovarian function cessation and age-related changes. Our objective was to investigate menopausal symptoms and knowledge among women aged 40-60 years.

Methods: This cross-sectional epidemiological study was conducted between June 1 and September 30, 2005, in the Nilufer Public Health Education and Research Area (NPHERA) region, aimed to assess menopausal symptoms and their correlates among 1013 women aged 40-60. The individuals included in the study were selected through a systematic sampling method, stratified by neighborhood weights and age groups based on the NPHERA 2004 Work Report and regional data, as well as information from the Health Centers Information System (HCIS), where the Electronic Health Records (EHR) are registered.

Results: The mean age of natural menopause was found to be 46.7±4.8 years, showcasing sociodemographic factors' influence. Postmenopausal women experienced higher rates of symptoms, with physical and mental exhaustion (82.8%), irritability (78.4%), and depressive mood (76.4%) prevailing. Logistic regression revealed that employment status significantly influenced menopausal status. Moreover, the age at menopause correlated positively with the age of the woman's mother.

Conclusion: This study contributes insights into menopausal experiences in developing countries, emphasizing the need for tailored healthcare approaches. Longitudinal investigations are warranted to comprehensively understand these associations and enhance women's quality of life during menopause.

Keywords: Menopause, mental symptoms, physical symptoms, perimenopausal, public health

Menopause, an inherent biological process, signifies a crucial life stage for women, marked by the cessation of ovarian functions and various age-related changes [1]. To diagnose menopause, a minimum of 12 consecutive months of amenorrhea is anticipated [2].

In developed countries, the average age of natural menopause is around 51-52, whereas in developing

countries, this age tends to be lower [3]. Reviewing the literature reveals that genetic, demographic, reproductive, and sociocultural factors may exert influence on the age of menopause [4-6].

In today's context, considering the average life expectancy, it is evident that a significant portion of women's lives is spent during the menopausal period. The hormonal changes occurring during menopause lead to various physical and psychological alterations in women [7]. During this phase, women may experience somatic complaints such as hot flashes and night sweats, as well as psychological symptoms like fatigue, irritability, and difficulty concentrating, alongside urogenital issues. While these symptoms vary in intensity among individuals, they often have a collective impact, reducing the overall quality of life for most women during the menopausal transition [8, 9].

This study aims to evaluate menopausal complaints among women in a developing country, identify factors influencing menopausal age, and contribute to the development of policies enhancing the quality of life during this significant phase of a woman's life.

METHODS

This cross-sectional epidemiological study was conducted between June 1 and September 30, 2005, in the Nilufer Public Health Education and Research Area (NPHERA) region. The primary objective was to investigate menopausal symptoms and knowledge among women aged 40-60 years. Prior to the commencement of the research, ethical approval was secured from the Bursa Uludag University Faculty of Medicine Research Ethics Committee (Approval No: 2005-14/36). Data collection took place at three Public Health Education and Research Centers affiliated with NPHERA, namely Fethiye PHERC, Alaaddinbey PHERC, and Özlüce PHERC.

Study Population

The target population consisted of 2533 women aged 40-60 years residing in NPHERA. A sample of 1013 women, representing 40% of the total population, was included in the study. The individuals included in the study were selected through a systematic sampling method, stratified by neighborhood weights and age groups based on the NPHERA 2004 Work Report and regional data, as well as information from the Health Centers Information System (HCIS), where the Electronic Health Records (EHR) are registered.

The sampling process began with stratifying neighborhoods based on the female population aged 40-60, further stratifying by age groups. Samples were selected using a random number table, with a 10% backup for each group. Survey forms were created, and a pilot study involving 50 women (half from urban and half from rural areas) was conducted to address observed issues. Postmenopause was defined as the absence of menstruation for a duration exceeding one year. Women who reported having menstruated within the past year were categorized as premenopausal.

Data Collection

For each woman in the sample, two questionnaire forms (Form A and Form B) were administered through home visits. Form A was filled out through face-to-face interviews, while Form B, containing the Menopause Rating Scale (MRS), was self-administered by women. Illiterate participants had questions read aloud, and their responses were recorded. In cases of absence during the initial visit, two additional attempts were made to contact the woman. If three visits were unsuccessful, replacement women from the reserve list were selected.

Questionnaire Content

Form A comprised 24 questions, designed to gather information on socio-demographic characteristics, fertility characteristics, age at menopause, factors influencing menopause, and women's knowledge and attitudes towards menopause. Form B contains the MRS, which has been translated into Turkish and validated [10]. This scale comprises 11 questions that assess psychological, somatic, and urogenital symptoms associated with the menopausal period. Each of the 11 items in the MRS employs a Likert-type scale with the following response options: 0: None 1: Mild 2: Moderate 3: Severe 4: Very severe.

Statistical Analysis

In this study, data analysis was performed using SPSS Version 13. The distribution of the data was assessed using the Kolmogorov-Smirnov test. Numerical variables were compared using the Student's t-test,

while categorical variables were analyzed using the chi-square and adjusted chi-square tests. For normally distributed data, the Pearson correlation coefficient was employed to conduct correlation analyses. To investigate the factors affecting menopausal status, logistic regression analysis was employed. The results were presented in the form of mean values, standard deviations for numerical variables, and percentages for categorical variables. A significance level of P< 0.05 was considered statistically significant.

RESULTS

A comprehensive examination was conducted on a total of 2533 women aged between 40 and 60 from the NPHERA. Out of this population, 1013 women, representing 40% of the entire cohort, were interviewed. The participants were drawn from three distinct PHERCs: Fethiye PHERC (n=676), Alaaddinbey PHERC (n=147), and Özlüce PHERC (n=190).

The mean age of the women was 48.2±5.9 years, with a median age of 48 years. Table 1 presents the sociodemographic characteristics of the women. Among different age groups, the 40-44 age group represented the highest proportion at 33.9% (n=343), while the 55-60 age group constituted the lowest at 16.1% (n=163). Notably, 42.3% (n=428) of the women were born in Bursa. In terms of education, a majority of the women were primary school graduates, accounting for 56.6% (n=573), while the illiteracy rate was 13.8% (n=140). Social security affiliation revealed that 17.1% of women (n=173) were not linked to any institution. Concerning marital status, 87.2% (n=883) of the women were married, 9.7% (n=98) were widowed or had a deceased spouse, and 1.3% (n=13) had never been married or were single. As per their self-perceived economic status, 89% (n=902) of the women considered it to be moderate (neither good nor bad). Employment statistics indicated that only 5.6% (n=57) of women were employed, while the majority, 94.4% (n=956), had no employment (see Table 1).

Within the total participant pool, 44.2% of women (n=448) were identified as being in the post-menopausal phase. Among these postmenopausal participants, 81.7% (n=366) had experienced natural menopause, 17.6% (n=79) had undergone surgical menopause, and the remaining 0.7% (n=3) had

reached menopause due to chemo/radiotherapy. For those who underwent a natural menopausal transition, the mean age at menopause was 46.7±4.8 years. In the broader context, considering all women in the study, the overall mean age for menopause was 45.9±5.3 years.

Table1. Socio-demograhic characteristics of participants

	n	%
Age groups (years)		
40-44	343	33.9
45-49	279	27.5
50-54	228	22.5
55-60	163	16.1
Birth place		
Bursa	428	42,3
Other	585	57,7
Education level		
Illiterate	140	13.8
Literate	67	6.6
Elementary	573	56.6
Middle school	127	12.5
High school	92	9.1
University	14	1.4
Social security status		
No social security	173	17.1
Social security	840	82.9
Martial status		
Single	13	1.3
Married	883	87.2
Widowed	98	9.7
Divorced	8	0.8
Separated	11	1.0
Socio-economic status		
Low	59	5.8
Middle	902	89.0
High	52	5.2
Occupation		
Employed	57	5.6
Unemployed	956	94.4
TOTAL	**1013**	**100.0**

Table 2. The current somatic, psychological, urogenital complaints of premenopausal and postmenopausal women according to menopause rating scale

	Premenapausal (n=565)	Postmenopausal (n=448)	P value
Hot flashes			
No	211 (37.3)	95 (21.2)	**<0.001**
Yes	354 (62.7)	353 (78.8)	
Heart disease			
No	239 (42.3)	175 (39.1)	0.29
Yes	326 (57.7)	273 (60.9)	
Sleep disorders			
No	239 (42.3)	131 (29.2)	**<0.001**
Yes	326 (57.7)	317 (70.8)	
Joint and muscle problems			
No	157 (27.8)	93 (20.8)	**0.009**
Yes	408 (72.2)	355 (79.2)	
Depressive mood			
No	147 (26)	92 (20.5)	**0.04**
Yes	418 (74)	356 (79.5)	
Irritability			
No	136 (24.1)	83 (18.5)	**0.03**
Yes	429 (75.9)	365 (81.5)	
Anxiety			
No	224 (39.6)	166 (37.1)	0.39
Yes	341 (60.4)	282 (62.9)	
Physical and Mental exhaustion			
No	112 (19.8)	62 (13.8)	**0.012**
Yes	453 (80.2)	386 (86.2)	
Sexual problems			
No	329 (58.2)	203 (45.3)	**<0.001**
Yes	236 (41.8)	245 (54.7)	
Urinary complaints			
No	366 (64.8)	271 (60.5)	0.16
Yes	199 (35.2)	177 (39.5)	
Vaginal dryness			
No	390 (69)	260 (58)	**<0.001**
Yes	175 (31)	188 (42)	

Values are given as n (%). Chi- square test was performed.

Table 3. The relationship between sociodemographic and clinical characteristics of women only entering menopause naturally and their menopasual age

	<45 y (n=100)	45-49 y (n=156)	>49 y (n=110)	P value
Education status*				
<5 years	33 (32)	28 (27.2)	42 (40.8)	**<0.001**
>5 years	67 (25.5)	128 (48.6)	68 (25.9)	
Marital status				
Unmarried	3 (50)	1 (16.7)	2 (33.3)	0.34
Married /other**	97 (26.9)	155 (43.1)	108 (30)	
Economic status				
Low	8 (47.1)	5 (29.4)	4 (23.5)	0.17
Middle/ High	92 (26.4)	151 (43.3)	106 (30.3)	
Occupation				
Occupied	3 (16.7)	10 (55.6)	5 (27.7)	**0.45**
Unoccupied	97 (27.9)	146 (42)	105 (30.1)	
Menarche age (years)				
<14	46 (30.1)	69 (45.1)	38 (24.8)	0.17
>14	54 (25.4)	87 (40.8)	72 (33.8)	
First pregnancy age (years)				
<20	41 (24.4)	70 (41.7)	57 (33.9)	0.27
>20	59 (29.8)	86 (43.4)	53 (26.8)	
Total child number				
<1	4 (30.8)	6 (46.2)	3 (23)	0.83
>1	96 (27.2)	150 (42.5)	107 (30.3)	
Mother's menopause age (years)				
<45	35 (40.2)	35 (40.2)	17 (19.6)	**<0.001**
45-49	24 (27.6)	49 (56.3)	14 (16.1)	
>49	20 (22.7)	32 (36.4)	36 (40.9)	
Tobacco use				
No	87 (26.5)	142 (43.3)	99 (30.2)	0.58
Yes	13 (34.3)	14 (36.8)	11 (28.9)	
Oral contraception				
No	77 (27)	123 (43.2)	85 (29.8)	0.92
Yes	23 (28.4)	33 (40.7)	25 (30.9)	

Values are given as n (%). Chi square test was performed.

*Elementary school (5 years in Turkey by law till year 1998)

**Other: widowed, divorced

Table 2 presents the menopausal complaints of pre/postmenopausal women as assessed by the MRS. Hot flashes, sleep disorders, joint and muscle problems, depressive mood, irritability, physical and mental exhaustion, sexual problems, and vaginal dryness were significantly higher in the postmenopausal group compared to the premenopausal group. Additionally, the remaining complaints exhibited a numerical increase in postmenopausal women, although these differences did not reach statistical significance (see Table 2).

Table 3 illustrates the relationship between the natural onset of menopause in women and their sociodemographic and clinical characteristics. A statistically significant difference was observed between the ages at which women experienced menopause and the ages at which their mothers underwent menopause (P<0.05) (see Table 3). Furthermore, a weak but statistically significant positive correlation was identified between the ages at which women naturally entered menopause and the ages at which their mothers experienced menopause among women who were aware of their mothers' menopausal ages (r=0.225, two-tailed P=0.01).

In the logistic regression analysis modeling the relationship between menopausal status and sociodemographic variables, no significant associations were found between a woman's educational level (less than primary school/primary school and higher), social security status (yes/no), marital status (never married/married, widowed, separated, or divorced), and economic status (poor/medium and good) with menopausal status (P>0.05). However, in the case of employment status (working/not working), it was observed that the odds of being in menopause were 0.44 times higher for working women compared to non-working women (95% CI 0.20-0.93; P<0.05).

In the logistic regression analysis incorporating the "age" effect, the association between women's menopausal status and their complaints based on the MRS was investigated (see Table 4). In this model, it was revealed that only irritability exhibited a statistically significant relationship with women's menopausal status (OR: 1.76, 95 % CI 1.04-2.98, P<0.05). This indicates that women in menopause were 1.76 times more likely to experience irritability (Table 4).

DISCUSSION

In this study encompassing 1013 women aged between 40 and 60 in both urban and rural areas of Turkey, who are in the peri/postmenopausal period, the average age of menopause for women was calculated. Factors influencing the age of menopause were analyzed, and menopausal symptoms were assessed through a questionnaire.

In our study, the average age of the cohort was 48.2±5.9, while the natural menopausal age for

Table 4. Logistic regression analysis of menopause and menopausal symptoms

	OR	CI 95%	P value
Hot flashes	1.25	0.79-1.98	0.42
Heart disease	0.77	0.50-1.55	0.12
Sleep disorder	1.41	0.91-2.17	0.25
Malaise	0.90	0.55-1.49	0.11
Irritability	1.76	1.04-2.98	**0.02**
Anxiety	0.86	0.55-1.33	0.29
Physical fatigue	0.85	0.50-1.47	0.83
Sexual problems	1.42	0.97-2.09	0.17
Urinary problems	0.92	0.62-1.36	0.22
Vaginal dryness	1.48	0.99-2.21	0.14
Joint muscle disorders	1.03	0.66-1.63	0.55

women was calculated as 46.7±4.8. It's worth noting that the reported average age for menopause is approximately 51 years in developed nations and ranges between 43 and 48 in developing countries [3, 11]. A systematic review indicates that the average age of menopause varies in different regions, with values reported as 50.1-52.8 in Europe, 50.5-51.4 in North America, and 43.8-53 in Latin America [12]. When specifically considering Turkey, previous studies have reported, similar to our study, an average natural menopausal age of 47.8±4.0 for the urban region and 47.4±3.7 for the rural region [6, 13].

Additionally, the incidence of menopause in the women included in our study was 44.2%. While the exact prevalence of menopause in Turkey is not fully known, the Turkey Demographic and Health Survey (TDHS) reported that among women aged 30 and above, 42% cited menopause or hysterectomy as reasons for not using family planning [14]. On the other hand, Pirincci and colleagues, in their study conducted in a rural region, reported a higher menopausal rate of 64.4% among women aged 40 and above compared to our study [6].

However, it's noteworthy that the mean ages of the women included in this study were higher than those in our study (51.3±9.4 vs. 48.2±5.9) [6].

Menopause, although a normal physiological phase in a woman's life, can be associated with specific physical, psychological, and sexual symptoms due to hormonal changes during this period. In our study, we assessed women's menopausal complaints using a valid scale, the MRS. When focusing on women's menopausal symptoms, the most prevalent among all reported complaints was physical and mental exhaustion, at 82.8%. This was followed by irritability at 78.4% and depressive mood at 76.4%. When categorized into somatic, psychological, and urogenital subheadings, the most frequently reported somatic complaints were joint and muscle problems, while in the psychological category, physical and mental exhaustion took precedence. In the urogenital domain, sexual problems were prominent. The most pronounced complaint in terms of intensity was hot flashes. In the Pan-Asia Menopause (PAM) study, a randomized controlled trial involving Asian women and focusing on menopausal symptoms, similar to our findings, muscle and joint problems were reported as the most common symptoms, with percentages of 76% in Korean women and 96% in Vietnamese women [15]. In another dataset from Ecuador, where women were assessed using MRS similar to ours, muscle and joint problems were reported as the most common symptom, with a prevalence of 77% [16]. On the other hand, in a Spanish study, the predominant symptoms experienced by menopausal women were reported as hot flushes (51.4%), insomnia (45.7%), and irritability (42.2%), respectively [17]. Additionally, in studies conducted on Western and African–American populations, the overall prevalence of menopausal symptoms was found to be generally higher than in Eastern countries [18, 19]. In this context, it can be asserted that ethnicity plays a role in shaping the experience of menopausal symptoms. The prevalence of specific menopausal symptoms may vary across different geographical regions. Regional variations in sociodemographic features and cultural differences might contribute to distinct perceptions of menopausal symptoms among women.

In our study, we explored sociodemographic factors and fertility characteristics that could impact the natural menopausal status in women. The age of menopause was observed to be later in individuals with less than 5 years of education. Similarly, when assessing employment status, despite the small number of employed women (n=18), non-working women exhibited a higher age of menopause. Daily working stress is believed to be associated with an earlier onset of menopause On the other hand, in another study investigating factors affecting the age of menopause, it was reported that as the level of education increased, the age of menopause also increased [4].

In the current study, we did not observe a statistically significant relationship between menopausal age and marital status or economic situation. Conversely, previous studies have reported that unmarried women tend to experience early menopause compared to those who are married or widowed [4, 5]. Similarly, previous reports have indicated that a higher socioeconomic level, and therefore, better nutritional conditions, are associated with a delayed onset of menopause [20]. In our study, the limited representation of never-married individuals (n=6) and those with a low socioeconomic status (n=6) among menopausal women might have resulted in inadequate calculations.

Among fertility characteristics that can impact the age of menopause are menarche age, parity, and the woman's age during her first/last pregnancy. In a study involving 262 women, Özdemir *et al*. [21] reported an association between early menarche and early menopause, while they found no significant relationship between parity and the age of the woman during her first pregnancy with menopausal age. In a study conducted in Poland, both menarche and parity were reported as factors associated with the age of menopause [22]. Pirincci *et al*. [6] stated in their studies that a woman's age being >40 during her last pregnancy is associated with entering menopause at a later stage. In our study, we did not observe an association between menarche age, parity, and the woman's age during her first/last pregnancy with the age of menopause. However, there was a correlation between the age of menopause and the age of the woman's mother at menopause. This finding aligned with other studies. Pirincci *et al*. [6] demonstrated that a higher age at menopause in the mother is associated with a delayed onset of menopause in the daughter.

In the study conducted by Özdemir *et al*. [21], it was noted that experiencing early menopause in both the mother and sisters contributes to an individual's likelihood of undergoing early menopause themselves [21]. At that rate, it could be thought that there is a genetic correlation between family members for the age of menopause.

Smoking is known to be a dose-dependent factor that increases the age of menopause [23]. In the present study, the number of women who smoked or had previously smoked was very low, so no association between smoking and menopausal age was noted.

Limitations

Our study has notable strengths, including a robust participant cohort, the application of a validated survey for evaluating menopausal symptoms, and a deliberate focus on women experiencing natural menopause when exploring factors affecting the age of menopause. On the other hand, there are limitations to consider, such as the cross-sectional nature of the study, which prevented the sampling of the entire population, and the partially self-reported nature of the survey. Recall bias in individuals' self-reported histories is a potential consideration. However, previous studies on the reproducibility of the age reported by individuals themselves in natural menopause have shown that the recall of menopausal age through memory is quite reliable [24].

CONCLUSION

In conclusion, our study revealed that in a developing country, the average age of natural menopause is 46.7±4.8. Menopausal age was found to be significantly associated with education, employment status, and the age of the woman's mother. Additional longitudinal studies are required to elucidate and further understand these associations. Additionally, the most common complaint during the menopausal period was physical and mental exhaustion, with hot flashes identified as the most severe symptom. It is crucial for healthcare professionals to identify the challenges women face during menopause, and planning educational and counseling services is important for alleviating the severity of these issues. Thus, women can lead a higher quality of life during this period by adopting effective coping mechanisms for the health problems they experience in menopause.

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Descemet membrane endothelial keratoplasty and penetrating keratoplasty in pseudophakic bullous keratopathy: comparison of visual outcomes, graft survival rates, and complications

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ABSTRACT

Objectives: To compare the outcomes of Descemet Membrane Endothelial Keratoplasty (DMEK) and Penetrating Keratoplasty (PK) in patients with pseudophakic bullous keratopathy (PBK).
Methods: Records of 51 eyes of 51 PBK patients (32 male, 19 female) who underwent PK (Group1=38 eyes) and DMEK (Group 2=13 eyes) were reviewed retrospectively. The two groups were compared for Best-corrected visual acuity (BCVA), graft survival rates, and complications.
Results: The mean age was 69.1 and 67.1 years in group 1 and group 2, respectively. First-year cumulative survival rates for group 1 and group 2 were 92.1% and 61.5%, respectively, and 89.1% and 51.3% in the second year (P=0.001 by log-rank test). At the last follow-up visit, 2.7% of Group 1 and 30.8% of Group 2 had a BCVA of 0.3 or better (P=0.004). Graft failure was observed in 12 eyes (31.6%) in group 1 and 8 eyes (61.5%) in group 2 (P=0.056). At the last examination, the rates of transparent grafts were 73.7% and 69.2% in group 1 and group 2, respectively (P=0.756). Postoperative glaucoma was observed in 4 eyes (30.8%) in the group 2 and 4 eyes (10.5%) in the group 1 (P=0.083). There was no significant difference between the two groups regarding other complications (P>0.05).
Conclusions: DMEK surgery offers a better visual outcome than PK for the treatment of PBK. Careful follow-up of patients is required in terms of glaucoma and graft failure after DMEK. Although the graft survival rate was lower in the DMEK group, a similar rate of graft transparency was achieved at the final examination with repeated DMEK surgery.
Keywords: Deep anterior lamellar keratoplasty, descemet membrane endothelial keratoplasty, penetrating keratoplasty, macular corneal dystrophy

Corneal endothelial cells prevent the passage of anterior chamber fluid into the corneal stroma and keep the cornea transparent. When the barrier and pump function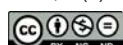 of the endothelium is disrupted and the endothelial cell density falls below the critical threshold due to various reasons such as endothelial dystrophy, surgical trauma, infection, eye trauma, glaucoma, and uveitis, excessive fluid accumulates in

the stroma. As edema increases, the cornea becomes cloudy, and painful bullae form in the epithelium. This condition is called Bullous keratopathy (BK) [1]. Bullous keratopathy is a common cause of corneal decompensation, often requiring corneal transplantation. Intraocular cataract surgery may cause or accelerate endothelial decompensation [2]. Corneal edema may develop after cataract surgery due to defects in the patient's endothelial number or structure or problems caused by surgery. If BK develops despite medical treatment, it is defined as pseudophakic bullous keratopathy (PBK), and surgical treatment is required. While painful and blind corneal tissue was replaced with full-thickness donor cornea until recent years, replacement of only the endothelial layer has now become a more common surgery [3]. However, penetrating keratoplasty (PK) is still used in advanced BK that develop chronic fibrosis or when endothelial keratoplasty (EK) is contraindicated.

Endothelial keratoplasty has advantages over PK, such as preserving the integrity of the eye, reducing risks such as postoperative astigmatism, suture problems, traumatic wound dehiscence, providing faster visual rehabilitation, and creating a predictable change in postoperative corneal power [4]. Despite these advantages, some complications such as high intraocular pressure (IOP) that can lead to graft failure are still encountered after EK [5]. Additionally, extensive corneal decompensation during EK can reduce the visibility of the graft in the recipient's anterior chamber.

The study aims to compare the postoperative visual results, complications, and graft survival rates of Descemet membrane endothelial keratoplasty (DMEK) and Penetrating keratoplasty (PK) in patients with PBK.

METHODS

The study was conducted by retrospectively reviewing the file records of patients who developed BK after cataract surgery with intraocular lens implantation (İOL) and underwent keratoplasty in a tertiary cornea clinic between 2010 and 2020. Records of 51 eyes of 51 PBK patients (32 male, 19 female) who underwent PK (Group 1=38 eyes) and DMEK (Group 2=13 eyes) (group 2) were reviewed. The hospital's ethics committee approved this retrospective study (Decision no.: 17/2024, Date: 21.02.2024) and the study adhered to the tenets of the Declaration of Helsinki.

Eligible subjects for the study were patients with subepithelial fibrosis, anterior stromal scarring, and corneal edema caused by corneal endothelial decompensation for more than 1year after cataract surgery. Inclusion criteria: Patients who were followed up for $\geq$1 year postoperatively, who were between the ages of 50-85, who had their first corneal transplant, who had not undergone eye surgery other than cataract, who did not have a systemic disease causing eye complications, and who did not have a history of chronic drug use were included in the study. Exclusion criteria: aphakic bullous keratopathy, being <50 years and >85 years of age, presence of fundus lesions affecting postoperative vision, and postoperative follow-up periods being less than 1 year.

Age, gender, follow-up period, postoperative complications, best-corrected visual acuity (BCVA) at the first year and the last examination, and whether the graft was transparent at the last examination were recorded from the patient's files. The data of the two groups were compared statistically. Graft survival rates were determined. Visual acuity was measured by Snellen charts was converted to logarithm of the minimum angle of resolution (logMAR) value for analysis. The BCVA of the two groups at the first year and at the last examination were recorded. Vision rates >0.3 and <1 were compared statistically between the two groups.

All donor corneas were examined for transparency and smoothness by slit lamp microscope. The morphology and number of endothelial cells were evaluated by specular microscopy. The density of all donors' corneal endothelial cells was >2.000/mm2. Intraocular pressure was measured with a Goldmann applanation tonometer. The following criteria were used to diagnose secondary glaucoma: IOP or estimated IOP$\geq$24 mmHg and need medication to lower it; postoperative IOP is 10 mmHg greater than the preoperative IOP. Translucent long-lasting ($\geq$ 1 year), irreversible corneal edema following surgery is referred to as primary graft failure.

Graft rejection was treated the same in both groups. The patient was hospitalized, and 1mg/kg systemic steroid (prednisolone) treatment and dexamethasone drops administered hourly were started. The dose was reduced according to the recovery status.

DMEK Surgery

All DMEK surgeries were carried out by the same surgeon (ZYA). First, the donor corneal endothelium obtained from the eye bank and planned to be transferred to the recipient's eye was prepared. For this, the donor corneal endothelium was stripped, stained with 0.06% trypan blue, and then suctioned into a DMEK syringe (DORC International BV) to insert the tissue into the anterior chamber. An 8-mm central area was marked on the recipient cornea to determine the desmatorexis border. The corneal epithelium was scraped with a crescent blade to increase visibility. The temporal and nasal side ports were opened with a 23-gauge blade. The anterior chamber was filled with air. Desmatorexis was performed using a reverse sinskey hook. The anterior chamber was entered through a 2.4 mm wide corneal tunnel at 12 o'clock in the upper cornea. The stripped endothelium was removed through the main incision. Air was evacuated from the anterior chamber. Iridectomy was performed with a vitrectomy probe at 6 o'clock. The donor corneal endothelium was injected into the anterior chamber through the main incision using the DMEK syringe. The endothelial roll was opened in the anterior chamber with the endothelium side down, using appropriate maneuvers. Air was injected under the endothelium through the side port. Postoperatively, broad-spectrum antibiotic drops were given 8 times a day and Dexamethasone drops 8 times a day for 2 weeks. Dexamethasone was gradually tapered and then loteprednol was given 4 times a day. It was tapered off at 6 months.

PK Surgery

The corneal tissue obtained from the eye bank was prepared by cutting it with a punch trephine to be 0.5 mm larger than the recipient bed. The center of the recipient's cornea was marked, and the edematous cornea was cut at the center with a vacuum trephine to a size of 7.25-7.75 mm (adjusted according to the corneal size). It was cut to full thickness with the help of side scissors and removed from the eye. The prepared donor corneal tissue was sutured to the recipient bed with continuous or interrupted sutures. Postoperatively, broad-spectrum antibiotic drops and Dexamethasone drops were given 8 times a day for 2 weeks. Dexamethasone drops were used gradually for 12 months.

Postoperatively, patients were examined on day 1,

week 1, and then at 1, 3, 6, 12, and 24 months. At each visit, data were collected by examining BCVA, IOP, graft status, lens, optic nerve head, and macula. Complications that developed and their treatments were recorded.

Statistical Analysis

The Shapiro-Wilk test was used to examine whether the data showed normal distribution. Categorical variables are presented as frequency and percentage, and continuous variables are presented as mean ± standard deviation. Categorical variables were compared with the Pearson Chi-square test. Normally distributed data were compared with independent samples t-test. Chi-square analysis was used to compare the complications between the two groups. Graft survival curves were generated with the log-rank test and using the standard Kaplan-Meier method. Statistical analyses were performed using IBM SPSS Statistics 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). P-values below 0.05 were regarded as significant.

RESULTS

The mean age was 69.13±9.68 and 67.15±10.59 years (P=0.538), and the mean follow-up period was 56.76±36.68 and 29.07±20.17 months (P=0.013) in group 1 and group 2, respectively. Gender ratios were similar in both groups (P=0.575) (Table 1). Graft rejection was seen in 12 eyes in group 1. Two eyes improved with treatment, but irreversible graft rejection occurred in 10 eyes. Irreversible graft rejection occurred in 1 eye in group 2. Graft failure was observed in 12 eyes (31.6%) in group 1 and in 8 eyes (61.5%) in group 2 (P=0.056). Endophthalmitis (2.6%), retinal detachment (2.6%), and postoperative ectasia (5.3%) were observed in low numbers only in the PK group. Postoperative glaucoma was observed in 4 eyes (10.5%) in the group 1 and 4 eyes (30.8%) in the group 2 (P=0.083). Pupillary block developed in 3 eyes in group 2 and IOP was regulated by postoperative air reduction and anti-glaucomatous medications. However, graft failure developed in these 3 eyes. In group 1, glaucoma was regulated with medications in 2 eyes, and glaucoma surgery was required in the other 2 eyes

Table 1. Demographic data of participants

	Group 1 (n=38)	Group 2 (n=13)	P value
Age (years)	69.13±9.68	67.15±10.59	0.538*
Gender, n (%)			0.575#
Male	23 (60.5)	9 (69.2)	
Female	15 (39.5)	4 (30.8)	
Follow-up (months)	56.76±36.68	29.07±20.17	**0.013***

Data are shown as mean±standard deviation or n (%).
#pearson chi-square test
*Independent samples t-test

(trabeculectomy in 1 eye, valve implant in 1 eye). There was no significant difference between the two groups regarding other complications (P>0.05). Re-grafting was made for 6 eyes (15.8%) in group 1 and 8 eyes (61.5%) in group 2 (P=0.001) (Table 2).

The BCVA rates of both groups at the first-year visit and the last follow-up visit are shown in Table 3. BCVA levels were better in Group 2 in both examinations (Table 3).

Graft survival Rates

Kaplan−Meier curves for graft survival in the two groups are presented in Fig. 1. The cumulative survival rates for PK and DMEK were 92.1% and 61.5% at 1 year and 89.1% and 51.3% at 2 years, respectively. Median survival time was 108 months in the group 1 and 42 months in the group 2 (P=0.001). At the last examination, the rates of transparent grafts were 73.7% and 69.2% in group 1 and group 2, respectively (P=0.756).

DISCUSSION

Bullous keratopathy after cataract surgery may be patient-related or caused by surgery. If existing endothelial numbers are low or endothelial changes such as Fuchs endothelial corneal dystrophy (FECD) are present, there is a risk of developing BK, even after an uncomplicated surgery. Endothelial decompensation may develop due to depletion such as using too much phaco energy during surgery, performing phacoemul-

Table 2. Comparison of complication rates between study groups

	Group 1 (n=38)	Group 2 (n=13)	P value*
Graft rejection, n (%)	10 (26.3)	1 (7.7)	0.159
Graft failure, n (%)	12 (31.6)	8 (61.5)	0.056
Glaucoma, n (%)	4 (10.5)	4 (30.8)	0.083
Keratitis n, (%)	6 (15.8)	2 (15.4)	0.972
Endophthalmitis, n (%)	1 (2.6)	0	0.555
RD, n (%)	1 (2.6)	0	0.555
Optic atrophy, n (%)	1 (2.6)	1 (7.7)	0.417
Postoperative ectasia, n (%)	2 (5.3)	0	0.399
Re-keratoplasty, n (%)	6 (15.8)	8 (61.5)	**0.001**

RD=Retinal detachment
*Pearson chi-square test

Table 3. Comparison of visual outcomes between groups

	Group 1 (n=38)	Group 2 (n=13)	P value*
1. year BCVA, n (%)			
>0.3	5 (13.2)	5 (38.5)	**0.047**
<1	24 (63.2)	6 (46.2)	0.282
Last visit BCVA, n (%)			
>0.3	1 (2.7)	4 (30.8)	**0.004**
<1	30 (78.9)	8 (61.5)	0.214

BCVA=Best-corrected visual acuity (logMAR)

*Pearson chi-square test

sification too close to the endothelium, the surgical instrument or cataract piece touching the endothelium, or severe toxic anterior segment syndrome (TASS). The preferred treatment for PBK in recent years has been EK, which permits selective replacement of the host endothelium rather than PK [6]. Studies on the effectiveness of PK [7] and EK [6, 8] after BK have been previously conducted. However, studies comparing the surgical results of PK and EK in PBK are limited [9-11]. In these studies, PK and Descemet
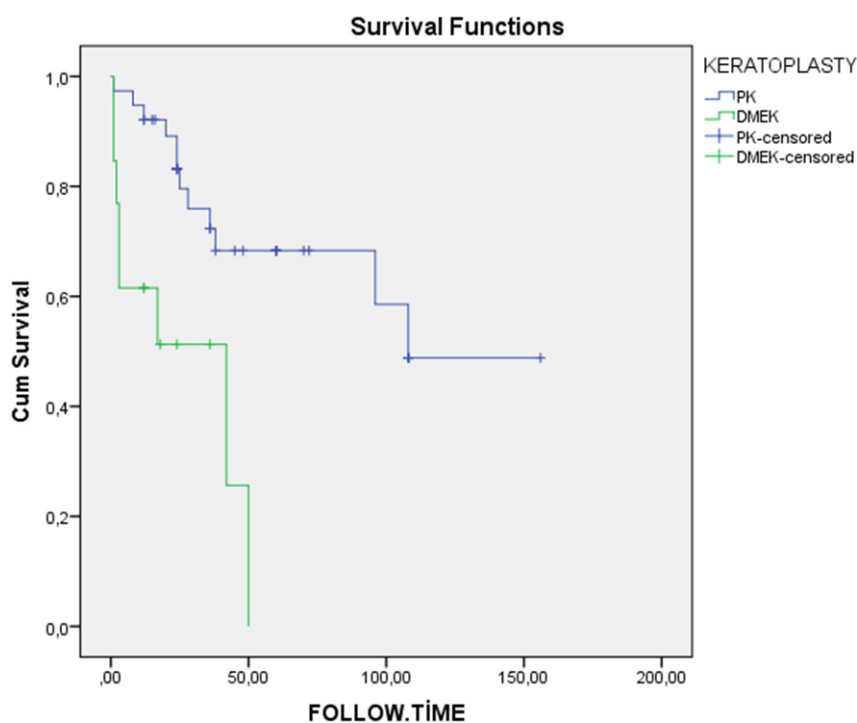
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	10.930	1	.001

Test of equality of survival distributions for the different levels of KERATOPLASTY.

Fig. 1. Comparison of graft survival rates between groups.

stripping endothelial keratoplasty (DSEK) were compared. To our knowledge, the current study is the first to compare PK with DMEK in PBK. In the current study, the differences between PK and DMEK surgeries in the treatment of PBK were evaluated in terms of visual outcomes, complications, and graft survival.

Since PK has been used in the treatment of BK for many years, the follow-up period was longer in the PK group. The rate of graft rejection is expected to be higher in PK compared to DMEK due to the entire corneal tissue change. In this study, although the rate was higher in the PK group, no statistically significant difference was detected between the two groups. Two other studies comparing PK and DSEK results in the BK also reported that graft rejection rates did not differ significantly [10, 11]. Although the difference was not significant in this study, graft failure was slightly higher in the DMEK group. We think that this is because the learning curve of DMEK surgery is high and the rate of graft failure due to endothelial loss may have increased in surgeries performed in the first years.

Previous studies have shown reduced IOP and steroid needs in EK compared to PK for up to 2 years postoperatively [12]. However, in this study, the glaucoma rate was slightly higher after DMEK, but the difference was not statistically significant (P=0.083). After surgery, an IOP elevation can be caused by several factors, including the use of viscoelastic, the reaction to steroids, damage to outflow mechanisms, loss of angle support, and angle closure as a result of synechiae [13]. In the study by Maier et al., the incidence of IOP elevation and glaucoma was found to be lower after DMEK than after DSEK and PK. In this study, steroid-induced IOP elevation was the most common cause [14]. In a study by Sharma et al., in eyes that underwent keratoplasty with different etiologies, IOP increase occurred at a lower rate in the early period after DSEK than in PK. However, there was no significant difference in IOP between the DSEK and PK groups at the 24th week [15]. In the study comparing the glaucoma therapy escalation (GTE) after PK and DSEK in eyes with PBK, no significant difference was found between the two groups [16]. In the current study, the most important reason for the high glaucoma rate after DMEK was the development of the pupillary block. If the air given to ensure adhesion of

the descemet to the recipient bed also closes the iridotomy, the pupillary block may develop. The IOP of these 3 eyes was regulated by reducing the amount of postoperative air and using anti-glaucomatous treatment. However, graft failure occurred because endothelial cells were affected. Although the IOP increased significantly after DMEK, none of them developed glaucoma surgery. However, in the PK group, glaucoma could be regulated by surgery in 2 patients. Since steroid treatment after DMEK is used for a shorter duration and in lower doses, steroid-induced IOP elevation is less expected than after PK surgery. Therefore, in long-term follow-up, the number of eyes with uncontrolled glaucoma requiring surgery after DMEK can be expected to be lower compared to the PK group.

Endophthalmitis, retinal detachment, and postoperative ectasia were observed only in the PK group. Although follow-up periods are different, the risk of endophthalmitis and retinal detachment is a less expected complication in DMEK surgery performed with a more closed system. However, since the entire cornea is opened in PK, the risk of these serious complications increases. Since tissue is not sutured in DMEK surgery, unlike PK, ectasia complications are not expected.

In this study, reDMEK surgery was performed in all 8 eyes that developed graft failure after DMEK. However, after PK, only 6 eyes underwent re-keratoplasty. This may be because replacing the endothelium alone is more advantageous and less risky than full-thickness surgery. Additionally, some patients could not undergo re-keratoplasty surgery because they did not want to have keratoplasty again or because it was thought that a new surgery would be risky due to other health conditions. As a result of these grafts, the transparent graft rates at the last examination were 73.7% and 69.2% in the PK and DMEK groups, respectively. In this study, BCVA levels were found to be significantly higher in the DMEK group at the first year and at the last visit. This is similar to previous studies [10, 11]. The astigmatism resulting from the sutures placed after PK and the altered anterior corneal surface curvature from the whole corneal alteration were considered to be the causes of the DMEK group's better visual acuity.

Contrary to previous studies, in this study, the

graft survival rate was found to be higher in the PK group. First-year cumulative survival rates for PK and DMEK were 92.1% 61.5%, and 89.1% and 51.3% at 2 years, respectively (P=0.001). The reason for this difference may be early graft loss due to endothelial loss during DMEK surgeries performed in the early years. In the study by Chen *et al*., at the last follow-up 1 year after surgery, the graft survival rate in the DSEK group was found to be significantly higher than that in the PK group (91.17% vs. 70.37%, P=0.039) [10]. In the study by Kim *et al*., the 2-year graft survival rates for DSAEK and PK were 93.3% and 81.8%, respectively, and the median graft survival was 56 and 44 months, respectively (P=0.344) [11]. In a similar study by Wai *et al*., 2-year survival rates for DSEK and PK were found to be 80.8% and 75%, respectively [9]. The difference between the studies may be due to less endothelial loss due to easier manipulation of the DSEK graft. Another reason may be that the number of patients in the groups differs in the studies. Manipulation of the endothelial roll in DMEK surgery is a little more difficult than in DSEK and DSAEK surgery. Therefore, until experience is gained during surgery, endothelial loss and subsequent graft failure may occur. To our knowledge, no study comparing DMEK and PK has been conducted before. Additionally, in this study, DMEK surgeries performed in the last year could not be included in the study because their follow-up period was short, and therefore the DMEK numbers are slightly low. For all these reasons, graft survival rates may have been different compared to other studies.

Limitations

There were some limitations of the current study. Due to the retrospective nature of the study, variables including patient selection, astigmatism adjustment following PK, and endothelial number comparison could not be assessed. The smaller number of patients in the DMEK group, the longer surgical time until experience in DMEK surgery was gained, and the higher rate of graft failure due to endothelial loss that may develop due to the high number of surgical manipulations, may have affected the results of the study. Therefore, prospective studies with more patients are required. However, we believe that this study can provide insight as a pioneering study and that better studies can be carried out by evaluating the deficiencies.

CONCLUSION

DMEK surgery offers a better visual outcome than PK for the treatment of PBK. However, care must be taken in terms of postoperative glaucoma and graft failure. Even though the DMEK group's graft survival rate was lower in the study, repeat DMEK surgery led to a comparable rate of graft transparency at the final assessment.

Ethical Approval

All procedures performed in study comply with the ethical standards of the Institutional research committee of the University of Health Sciences Ankara Training and Research Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Authors' Contribution

Study Conception: ATB, ND, AB, ZYA, EŞ, SU; Study Design: ATB, ND, AB, ZYA, EŞ, SU; Supervision: ATB, ND, AB, ZYA, EŞ, SU; Funding: ATB, ND, AB, ZYA, EŞ, SU; Materials: N/A; Data Collection and/or Processing: ND; Statistical Analysis and/or Data Interpretation: ATB; Literature Review: ATB; Manuscript Preparation: ATB and Critical Review: ZYA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Comparison of the effect of erector spinae plane block for postoperative analgesia on neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients operated for breast cancer

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ABSTRACT

Objectives: It was seen that recurrence and metastasis after breast cancer surgery are related to the immune response of the host. Anesthetic agents modulate the surgical stress response or directly impair the functions of immune system cells. In our study, we aimed to compare the effects of nonsteroidal anti-inflammatory drugs and erector spinae plane block, which are among the methods we use for postoperative analgesia, on the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients undergoing breast cancer surgery.
Methods: One hundred female patients aged 18-75 years, scheduled for unilateral breast cancer surgery, and who agreed to participate were included in our study. These cases were divided into two groups of the analgesia method: Those with erector spinae plane block (Group E) and those who were administered nonsteroidal anti-inflammatory drugs (Group N). According to the results, preoperative and postoperative neutrophil/lymphocyte ratio and platelet/lymphocyte ratio values were calculated and recorded.
Results: Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were statistically higher in both groups in the postoperative period. No statistically significant difference was found when the preoperative and postoperative measurement changes of the laboratory parameters between the groups were compared. Postoperative VAS scores were statistically significantly lower in Group E.
Conclusions: We concluded that when erector spinae plane block and nonsteroidal anti-inflammatory drug use were compared in managing postoperative analgesia in breast cancer surgery, their effects on the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were not superior to each other. However, the erector spinae plane block was superior for adequate pain control.
Keywords: Breast cancer, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), erector spinae plane block (ESPB), stress response

*W*omen's breast cancer is the fifth leading cause of worldwide cancer deaths and constitutes 11.7 % of all cancer cases [1]. The reactions of immune system cells to breast cancer are associated with the prognosis and mortality of cancer. Although immune surveillance provides an important first defense against cancer cells, it can be associated with tumor growth by changing tissue microchexes [2]. It is suggested that the increase in the number of neutrophils in these patients is correlated with poor prognosis. Neutrophils remodel the tumor microenvironment and suppress the cytolytic activity of the host immune system. It has been shown that neutrophils in peripheral blood secrete inflammatory mediators that cause tumor growth. Unlike neutrophils, the presence of lymphocytes in tumor tissue is associated with healing and good prognosis in breast cancer patients. Lymphocytes in the tumor microenvironment are thought to fight tumor cells in the host by inhibiting the growth and migration of tumor cells [3]. It is known that platelets directly interact with tumor cells and secrete the factors contributing to tumor growth, invasion, and angiogenesis. Thrombocytes can protect tumor cells from natural lethal cell-mediated lysis and facilitate metastasis [4].

It is known that surgical procedures and anesthesia practices indirectly affect the inflammatory response process by modifying the stress response or directly disrupting the functions of immune system cells. It has been reported that intravenous anesthetics, inhalation anesthetics and opioids used in general anesthesia induction and maintenance suppress the immune system and increase cancer recurrence in oncological surgery [5].

Recently, oncological surgery, there is a positive effect on survival and metastasis, but has been ordered to regional anesthesia and analgesia techniques that have not yet been consensive [6, 7]. It is thought that the sympathetic blockage formed after the erector spinae plane block (ESPB) for postoperative analgesia of breast cancer surgery suppresses the hemodynamic response of surgical stress [8].

Neutrophil/lymphocyte ratio (NLR) is used as a marker of subclinical inflammation. The stress of leukocytes in the organism, the increase in the number of neutrophils, the number of lymphocytes in the form of a decrease in the physiological response has been shown as a result of the researches. Cellular immunity has an important place in tumor progression. The presence of T lymphocytes in tumor tissue is a significant indicator of the immune response to the tumor. The number of high neutrophils shows the activation of the proinflammatory immunity pathway, and low number of low lymphocytes reflects that cellular immunity is suppressed [9].

Platelet/lymphocyte ratio (PLR) has recently been associated with inflammatory response and immune system like NLR, and has become a prognostic marker in many solid organ tumors. High PLR values were found to be directly related to survival in solid organ tumors such as breast, pancreas and ovarium [10]. As a result of all this, NLR and PLR have taken its place in the literature as cheap, and easy accessible biobelirts.

Our aim in our study; in patients with breast cancer surgery, general anesthesia and nonsteroid antiinflammatory drugs (NSAID) and ESPB, which we use routine for analgesia, to compare the effect of ESPB on NLR and PLR.

METHODS

The study was started with the approval of Namık Kemal University Hospital Clinical Research Ethics Committee (dated 27.10.2020 and decision number 2020.234.10.02). The study was planned as prospective, randomized and single-blind in female patients aged 18-75 who would undergo unilateral elective breast surgery, with the consent of the patients. Anticipating a large effect size (effect size=0.8) difference between the groups, the alpha (α) significance level was 0.05 and the sample size for 95% Power was calculated as 100 people. Patients planned for bilateral mastectomy and lymph node dissection, those with known hematological malignancies, those in pregnancy and puerperium, patients with evidence of active infection in the planned block area, existing coagulopathy, emergency cases, severe organ failure and local anesthetic allergy were excluded from the study.

Randomization was achieved by sealed envelope method. The patients were divided into two: cases to be administered intravenous NSAID (Tenoxicam), one of the methods routinely used for postoperative anal-

gesia (Group N, n=50), and cases to be subjected to ESPB (Group E, n=50). In both groups, demographic data (age, weight, height, BMI), operation time and ASA score were recorded. A tube of blood was taken from all cases into a purple-capped hemogram tube before the operation. In the hemogram analysis, the patients' white blood cell (WBC), leukocyte, lymphocyte, platelet, hemoglobin, hematocrit, mean body volume (MCV), and mean platelet volume (MPV) measurements were recorded. According to the results, NLR and PLR values were calculated and recorded. The patients who would undergo ESPB (Group E) were taken to the waiting room 30 minutes before the operation. All cases were monitored with electrocardiography (ECG), pulse oximetry (SpO_2) and noninvasive blood pressure (NIBP) measurement cuff before general anesthesia, and their vital parameters [heart rate peak (HR), SpO_2, NIBP] were recorded before the operation.

Anesthesia Technique

Routine monitoring (ECG, NIBP and SpO_2) was applied to all patients taken to the operating table. General anesthesia was induced with Propofol 2-3 mg/kg, Fentanyl 1-2 mcg/kg, Rocuronium 0.6 mg/kg intravenously. After muscle relaxation, all patients were orotracheally intubated with an appropriate size laryngoscope. After induction, anesthesia was maintained with 2 L/min flow, 50% oxygen-air mixture, Sevoflurane 2%. Tenoxicam 20 mg was administered intravenously to patients in Group N after anesthesia induction and intubation. At the end of the operation, Atropine 0.01 mg/kg and Neostigmine 0.03 mg/kg were administered intravenously to both groups to reverse the neuromuscular blockade effect.

Analgesia Technique

The block application was performed by an experienced anesthesiologist (who had performed this block at least 20 times), independently of the study, under the guidance of an ultrasonography device (Esaote MyLabX7, United Kingdom). The level of the 4th thoracic vertebra was taken as the block level. The peripheral nerve block needle (Stimuplex Ultra 360® Braun, Germany, 22 gauge, 50 mm) was directed from cranial to caudal under ultrasonography guidance, and when it passed the erector spinae muscle and contacted the transverse process, it was withdrawn slightly and

20 ml 0.25% bupivacaine was injected into the confirmed space (Fig. 1). At the 30th minute after the block, dermatome mapping was performed with a hot-cold test and the patients were taken to the operating table.

Visual analoug scale (VAS) scores of all patients taken to the recovery unit for postoperative care were recorded. Patients were sent to the surgery service when the Modified Aldrete score was 9. A tube of blood was collected from both groups in a purple-capped hemogram tube at the 2nd postoperative hour. Hemogram parameters (WBC, leukocyte, lymphocyte, platelet, hemoglobin, hematocrit, MCV, MPV, NLR, PLR) were recorded. VAS scores of all patients participating in the study were recorded at 0, 2, 4 and 6 hours.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used when evaluating the study data. The suitability of quantitative data for normal distribution was tested using the Shapiro-Wilk test and graphical analysis. Independent groups t test was used to compare normally distributed quantitative

Fig. 1. Erector spinae plane block block needle placement and local anesthetic spread. LA=Local anesthetic.

Table 1. Demographic (Age, weight, height, bmi) data of the cases according to analgesia types

		Group E (n = 50)	Group N (n = 50)	P value
Age (years)		52.54 (25-75)	51.92 (26-75)	0.784[a]
Weight (kg)		76.36 (44-115)	77.06 (47-109)	0.820[a]
Height (m)		1.61 (1.52-1.75)	1.61 (1.50-1.72)	0.639[a]
BMI (kg/m^2)		30.16 (17.2-49.8)	29.23 (18.4-39.4)	0.459[a]
Surgical side	Right	23 (46.0)	26 (52.0)	0.548[e]
	Left	27 (54.0)	24 (48.0)	
Surgery time (min)		113.42 (45-175)	118.34 (70-195)	0.883[a]

Descriptive statistics are given as mean (minimum-maximum) depending on the distribution for numerical variables, and as number (%) for categorical variables. Group E=those with erector spinae plane block, Group=those who were administered nonsteroidal anti-inflammatory drugs, BMI=Body Mass Index.
[a]Student t test, [e]Pearson Chi-Square test

variables between two groups, and Mann-Whitney U test was used to compare non-normally distributed quantitative variables between two groups. Friedman Test was used for intragroup comparisons of quantitative variables that did not show normal distribution, and Wilcoxon signed-ranks test with Bonferroni correction was used for evaluation of pairwise comparisons. Dependent groups t test was used for intragroup comparisons of normally distributed quantitative variables. Wilcoxon signed-ranks test was used for intragroup comparisons of quantitative variables that did not show normal distribution. Pearson chi-square test was used to compare qualitative data. Pearson correlation analysis and Spearman correlation analysis were used to evaluate the relationships between quantitative variables. Statistical significance was accepted as $P<0.05$.

RESULTS

The average age of the cases participating in the study was 52.23±11.21, average body weight was 76.71±15.25 kg, average height was 1.61±0.06 m, average BMI was 29.69±6.23 kg/m2. has been determined. The distribution of age, weight, height and BMI between the groups was found to be statistically insignificant (P=0.784, P=0.820, P=0.639 and P=0.459, respectively) (Table 1).

Fourty-nine percent (n=49) of the cases had surgery for right breast cancer, and 51% (n=51) had surgery for left breast cancer (Table 1). The average operation time was 113.42 minutes in Group E (n=50) and 118.34 minutes in Group N (n=50), and there was no significant difference between the groups (P=0.883) (Table 1).

Table 2. Comparison of vital parameters of patients in group E and group N in the preoperative period

Preoperative period	Group E (n=50)	Group N (n=50)	P value[a]
HR	72.22 (53-96)	72.12 (53-98)	0.695
SpO$_2$	97.92 (94-100)	97.88 (94-100)	0.706
MAP	77.66 (64-95)	78.92 (60-96)	0.162

Descriptive statistics are given as mean (minimum-maximum) depending on the distribution for numerical variables. Group E=those with erector spinae plane block, Group=those who were administered nonsteroidal anti-inflammatory drugs, HR=Heart rate peak, SpO$_2$=Oxygen saturation, MAP=Mean arterial pressure.
[a]Student t test

Table 3. Evaluation of laboratory parameters according to analgesia types

	Group E (n = 50)	Group N (n = 50)	P value
WBC (/µL)			
Preoperative	7485.60 (4330-28620)	6458.66 (2900-10650)	0.334[b]
Postoperative	10127.60 (4810-19300)	9836.80 (4530-21500)	0.738[b]
P value	**[c]0.001****	**[c]0.001****	
Δ(Preop-Postop)	2642.00 (35.20)	3378.14 (52,30)	0.918[b]
Leukocyte (/µL)			
Preoperative	4586.72 (2140-24500)	4110.00 (850-7470)	0.754[b]
Postoperative	8313.00 (3360-17300)	8257.60 (3550-18600)	0.929[a]
P value	**[c]0.001****	**[c]0.001****	
Δ(Preop-Postop)	3726.28 (81.20)	4147.60 (100,90)	0.989[b]
Lymphocyte (/µL)			
Preoperative	2082.26 (610-4620)	2061.80 (700-4580)	0.310[b]
Postoperative	1249.72 (530-2530)	1382.20 (450-2560)	0.424[b]
P value	**[c]0.001****	**[c]0.001****	
Δ(Preop-Postop)	-832.54 (39,90)	-679.60 (32.96)	0.442[b]
Platelet (×10^{9}/L)			
Preoperative	276300.0 (153000-452000)	264500.0 (154000-400000)	0.067[a]
Postoperative	240960.0 (138000-446000)	239780.0 (105000-424000)	0.099[b]
P value	**[c]0.001****	**[c]0.001****	
Δ(Preop-Postop)	-35340.0 (12.79)	-24720.0 (9.34)	0.637[b]
MPV (fL)			
Preoperative	8.51 (7.3-10,1)	8.72 (3-10.8)	0.114[b]
Postoperative	8.47 (7-10.2)	8.91 (6.9-11.5)	**0.049*[b]**
P value	0.800[c]	0.166[c]	
Δ(Preop-Postop)	-0.03 (0.35)	0.19 (2.17)	0.269[b]
NLR			
Preoperative	2.53 (0.8-10.4)	2.65 (0.6-8.8)	0.122[b]
Postoperative	7.81 (1.7-27)	9.00 (2.1-22.7)	0.182[a]
P value	**[c]0.001****	**[c]0.001****	
Δ(Preop-Postop)	5.28 (208.69)	6.35 (239.62)	0.212[b]
PLR			
Preoperative	155.28 (64.7-616.4)	155.86 (91.1-431)	0.497[b]
Postoperative	223.67 (84.6-564.6)	245.13 (65.2-533.9)	0.236
P value	**[c]0.001****	**[c]0.001****	
Δ(Preop-Postop)	68.39 (44.04)	89.26 (57.26)	0.279[b]

Descriptive statistics are average (minimum-maximum) depending on the distribution for numerical variables; for categorical variables, it was given as number (%). Group E=those with erector spinae plane block, Group=those who were administered nonsteroidal anti-inflammatory drugs, WBC=White blood cell, MPV=Mean platelet volume, NLR=Neutrophil/Lymphocyte ratio, PLR=Platelet/Lymphocyte ratio, Preop=Preoperative, Postop=Postoperative.
[a]Student t test, [b]Mann Whitney U test, [c]Wilcoxon Signed Rank test, *P<0.05, **P<0.01.

The vital parameters of all cases were measured when they were taken to the waiting room before the operation, and there was no statistically significant difference between the mean arterial pressure calculated from the HR, SpO2 and NIBP measurements of the groups (P=0.695, P=0.706 and P=0.162, respectively) (Table 2).

When the laboratory data of the cases are examined; Postoperative WBC and leukocyte counts increased statistically significantly in both groups (P=0.001 and P=0.001, respectively). When the postoperative WBC and leukocyte count increases were compared between the groups, although the increase observed in Group N was numerically higher than the patients who underwent ESPB, no statistically significant difference was found between the two groups (P=0.918 and P=0.989, respectively) (Table 3).

A decrease in postoperative lymphocyte and platelet counts was detected in both groups, and it was found to be statistically significant (P=0.001 and P=0.001, respectively). When the decrease in the lymphocyte and platelet counts of the cases in the postoperative period was compared between the groups, no

statistically significant difference was found (P=0.442 and P=0.637, respectively) (Table 3).

Postoperative MPV measurements of those who received analgesia with ESPB were found to be statistically significantly lower than those who received analgesia with NSAIDs (P<0.05). No statistically significant difference was detected between the MPV measurement changes of the cases according to analgesia types (P=0.269) (Table 3).

Preoperative and postoperative period NLR measurements of the cases do not show a statistically significant difference according to analgesia types (P=0.122 and P=0.182, respectively). The average increase of 5.28±4.01 units in the postoperative NLR measurements of the patients in Group E compared to the preoperative period was found to be statistically significant (P=0.001; P<0.01). The average increase of 6.35±4.66 units in the postoperative NLR measurements of the patients in Group N compared to the preoperative period was found to be statistically significant (P=0.001; P<0.01). Although the increase in NLR that we observed in patients who received analgesia with nonsteroidal anti-inflammatory drugs

Table 4. Evaluation of postoperative visual analog scale measurements according to analgesia types

Postoperative	Group E (n=50)	Group N (n=50)	P value
VAS 0	4.16 (1-7)	5.50 (2-8)	[a]0.001**
VAS 2	3.64 (1-6)	4.62 (2-7)	[a]0.001**
VAS 4	3.32 (1-6)	4.16 (2-8)	[a]0.003**
VAS 6	2.92 (1-6)	3.56 (2-6)	[a]0.013*
P value	[e]0.001**	[e]0.001**	
Δ			
0-2	-0.52	-0.88	[b]0.171
P value	[ee]0.199	[ee]0.004**	
0-4	-0.84	-1.34	[b]0.031*
P value	[ee]0.001**	[ee]0.001**	
0-6	-1.24	-1.94	[b]0.005**
P value	[ee]0.001**	[ee]0.001**	

Descriptive statistics for numerical variables were provided in terms of distribution, including the mean (minimum-maximum) format. Group E=those with erector spinae plane block, Group=those who were administered nonsteroidal anti-inflammatory drugs, VAS=Visual Analog Scale, VAS 0=Visual Analog Scale score at 0 hours, VAS 2=Visual Analog Scale score at 2 hours, VAS 4=Visual Analog Scale score at 4 hours, VAS 6=Visual Analog Scale score at 6 hours.
[a]Student T Test, [b]Mann Whitney U Test, [e]Friedman Test & [ee]Wilcoxon tet, *P<0.05, **P<0.01

was numerically higher than in patients who underwent ESPB, no statistically significant increase was detected (P=0.212) (Table 3).

Preoperative and postoperative period PLR measurements of the cases do not show a statistically significant difference according to analgesia types (P=0.497 and P=0.236, respectively). The average increase of 68.39±108.89 units in the postoperative PLR measurements of the patients in Group E compared to the preoperative period was found to be statistically significant (P=0.001 and P<0.01, respectively). The average increase of 89.26±110.17 units in the postoperative PLR measurements of the patients in Group N compared to the preoperative period was found to be statistically significant (P=0.001and P<0.01, respectively). No statistically significant difference was detected between the PLR measurement changes of the cases according to analgesia types (P=0.279) (Table 3).

The VAS measurements at 0, 2, 4, and 6 hours in Group E patients were statistically significantly lower compared to those in Group N patients (P=0.001, P=0.001, P=0.003, P=0.013 and P<0.05, respectively). The changes in VAS measurements at 4 hours and 6 hours compared to hour 0, for patients provided analgesia with nonsteroidal anti-inflammatory drugs (NSAIDs), were statistically significantly higher than those undergoing analgesia with Erector Spinae Plane Block (ESPB) (P=0.031, P=0.005 and P<0.05, respectively) (Table 4).

DISCUSSION

Breast cancer is the second most common cause of cancer-related deaths worldwide. [1]. The primary reason for this high mortality rate is local recurrence and metastases, despite the best surgical treatment. Surgery is generally the preferred and curative method in breast cancer treatment. However, tumor cells have a tendency to undergo micrometastasis in the blood and lymphatic circulation that cannot be controlled during surgery. At this point, the host immune defense becomes crucial. It is believed that analgesic and anesthetic methods minimizing the stress response and suppressive effects on the immune system of surgery may have a positive impact on recurrence and metastases.

The immune system cells present in the tumor mi-

croenvironment undergo reshaping in response to surgical stress-induced inflammation. As a result of inflammation, the number of neutrophils increases, while the counts of lymphocytes and natural killer cells decrease within the tumor microenvironment. It is believed that the decreased cytotoxic-effective cells and the cytokines released by inflammatory mediators trigger tumor growth and metastasis [11].

In a study where Lombardi *et al*. [12] investigated postoperative inflammatory parameters, hematological parameters in the postoperative period were examined. White blood cell (WBC) count, leukocyte percentage, lymphocyte percentage, and mean corpuscular volume (MCV) were found to be statistically significantly higher compared to the preoperative period in all cases. In the same study, hemoglobin, hematocrit, and platelet count were found to be statistically significantly lower compared to the preoperative period in all cases. Consistent with this study, in our study, a statistically significant increase in WBC and leukocyte counts was observed in all cases during the postoperative period, while a statistically significant decrease in lymphocyte, platelet, hemoglobin, and hematocrit levels was also found. We believe that the increase in WBC and leukocyte counts and the decrease in lymphocyte and platelet counts observed in the postoperative period are related to immune modulation resulting from the surgical stress response.

Studies have demonstrated the immunosuppressive role of general anesthesia. Anesthetic agents can suppress cell-mediated immunity or induce an alteration in the balance between proinflammatory and anti-inflammatory cytokines. Additionally, acute pain also plays a suppressive role on the immune system [13].

Breast cancer surgery is one of the surgeries where postoperative pain incidence and opioid consumption increase due to the complex innervation network of the breast. The intensity of postoperative pain has a significant effect on the chronicization of pain. Increased opioid dependence due to pain is an undesirable behavior in cancer patients. The suppressive effect of opioids on cellular and humoral immunity has been known for many years. Because of these effects, the use of regional blocks in breast cancer surgery and postoperative analgesia management has gained a significant place [14]. Regional anesthesia can reduce surgical stress and pain in the perioperative period, improving neuroendocrine function and cytokine-asso-

ciated stress response.

The implementation of an effective analgesia method can reduce the stress response to surgery in the perioperative period and is known to have a certain protective effect on the patient's immune system function. Hu *et al*. [8], in their study comparing the effects of ESPB and Paravertebral Block (PVB) on immune functions and postoperative recovery in breast cancer patients, observed lower VAS scores and higher levels of serum CD4, CD8, and IFNγ in the ESPB group. CD4+ T lymphocytes have a regulatory role over other lymphocytes. The preservation of the levels of CD4+ T lymphocytes, which are expected to decrease due to the stress response to surgery, in patients treated with ESPB compared to those treated with PVB, suggests that ESPB has less impact on immune functions.
To date, there is no precisely defined clinical threshold value for NLR in the studies conducted. Since the values found in current studies are associated with patient prognosis, we did not utilize these values in our study. Parallel to our literature review, we have come to the conclusion that high values of NLR may be associated with the immunosuppressive effect of the analgesic method we used.

For the Platelet/Lymphocyte Ratio (PLR), there is no clinically established critical threshold value. Krenn-Pilko *et al*. [15] and Gündüz *et al*. [16] have explained that a high PLR value is associated with poor prognosis. In our study, we believe that high PLR values may be related to the negative impact of the analgesia method on the immune system.

Erector spinae plane block's effectiveness is dependent on inter-compartmental spread and the distribution of local anesthetic near the targeted nerves. The absorption and diffusion of local anesthetic are crucial in determining the quality of the block. This is because the mechanism of action of ESPB is thought to involve the diffusion of the administered local anesthetic from the intertransverse ligament to the thoracic paravertebral space and its spread anteriorly, exerting an effect on the dorsal and ventral rami of the spinal nerves. The craniocaudal distribution of the local anesthetic is also important in terms of covering the surgical area. This distribution in the interfascial plane is dependent on the volume of the administered local anesthetic.

In studies conducted to date, various volumes of local anesthetic have been tested for Erector Spinae Plane Block (ESPB); however, the optimal volume,

concentration, and dermatomal distribution have not been defined yet. Abdella *et al*. [17], comparing the analgesic efficacy and patient satisfaction between two groups of patients undergoing ESPB with different volumes of local anesthetic, did not observe a statistically significant difference. However, when they visualized the craniocaudal spread of the local anesthetic using computed tomography with simultaneous administration of radiopaque contrast, they observed that bupivacaine applied in a high volume spread 22% more levels than the standard volume. Nevertheless, in the study, there was no statistically significant difference in the spread of the local anesthetic to the paravertebral space, epidural space, or spinal nerve roots with high volume application. However, the spread to the paravertebral space was observed in 30% of patients with a standard dose and 40% of patients with a high dose. Altıparmak *et al*. [18] conducted a study comparing different doses with the same volume. The group receiving a high dose of bupivacaine showed a greater decrease in postoperative Numerical Rating Scale (NRS) scores and opioid consumption.

In our study, we administered 20 ml of 0.25% concentration bupivacaine with 50 mg in standard volume at the T4 level to the group undergoing the block. We ensured control of the dermatomal region necessary for postoperative analgesia within the surgical area using a hot-cold test. In our study investigating the effect of the administered Erector Spinae Plane Block (ESPB) on postoperative NLR and PLR values, we did not find a statistically significant difference. We believe that the lack of statistically significant results may be associated with the standard volume we applied. The immunomodulatory effect of ESPB is known to be associated with the spread of the local anesthetic to the paravertebral and epidural spaces [19]. Therefore, we believe that by applying a higher volume, both increasing the spread to the paravertebral and epidural spaces and expanding the dermatomal area in the craniocaudal direction to reduce postoperative pain may lead to more effective results on the immune system.

Opioids are among the most frequently prescribed medications for cancer patients. There is a controversial relationship between opioids and the immune system. Several studies have shown that opioids inhibit the activity of immune cells [20, 21]. Chen *et al*. [22], in a study examining the impact of perioperative opi-

oid use on the immune system, administered opioid-based analgesia to one group and thoracic paraverte-bral block (PVB) to another group in 80 patients undergoing thoracoscopic lobectomy. They compared postoperative NLR values between the two groups. In the PVB group, the NLR value was significantly reduced on the 3rd day compared to the 1st day of surgery, which was statistically significant when compared to the opioid group.

When examining nonsteroidal anti-inflammatory drugs (NSAIDs), recent studies suggest a significant decrease in the development of breast cancer associated with these drugs [23, 24]. Forget *et al*. [25], who investigated the effect of NSAIDs in breast cancer patients with NLR > 4, found that perioperative NSAID use extended survival time and reduced the risk of recurrence by two-fold. In our study, although postoperative NLR and PLR values in the group where ESPB was applied showed a less pronounced increase compared to the other group, this was found to be statistically insignificant. Unlike many other practices, we believe that the limited perioperative opioid use in our study and the follow-up of patients with NSAIDs intraoperatively and perioperatively might result in the immune system being less affected compared to situations involving opioid use.

The erector spinae plane block (ESPB), in terms of its technique, is considered a safer block for providing analgesia to the breast compared to other blocks due to the absence of vascular and neural structures near the application site and its distance from the pleura. In our study, we did not observe any complications associated with ESPB application.

It is believed that analgesics and anesthesia methods used during the perioperative period play a significant role in the immune system and indirectly affect tumor progression. In our study, where we used easily accessible and cost-effective NLR and PLR values as parameters to observe this effect, although there was no statistically significant difference, we found that ESPB resulted in less neutrophilia and lymphopenia. We are of the opinion that further studies are needed to observe the reflection of this effect on the tumor microenvironment and the evasion of tumor cells from the immune system more clearly.

In our study, we believe that our preference for non-steroidal anti-inflammatory drugs (NSAIDs) in analgesic drug selection for patients compared with ESPB in our study is a limiting factor due to the significant effects of this drug group on cytokines associated with surgical stress response and inflammation. Additionally, we have come to the conclusion that other limiting factors may include not making a distinction between patients who have received neoadjuvant chemotherapy and those who have not, as well as not knowing the long-term outcomes of patients when selecting them for the study.

CONCLUSION

As a result, we observed that the use of ESPB in postoperative analgesia management in breast cancer surgery, compared to NSAIDs, did not create a significant difference in the surgical stress response. We observed that the effects on NLO and PLO, which we used as biomarkers for surgical stress response, did not show a significant difference. Although both analgesia options are effective methods in the postoperative period, we observed that ESPB provides more effective pain control.

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Determining the awareness of surgical nurses regarding frail patients: a cross-sectional study

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ABSTRACT

Objectives: The objective of this study is to determine the knowledge level and awareness of surgical nurses about fragile patients.
Method: Obtained through Introductory Information Survey Form created by the researchers and Fragile Patient Information Evaluation Form methods.
Results: The average age of the surgical nurses participating in the study was 28±5.01 years, the average professional experience was 5±5.09 years, and the average experience in the service they worked in was 3±2.83 years. The rate of those who heard the term 'frailty' for the first time is 63%. It was stated that 92.7% of the 110 surgical nurses participating in the study did not receive any training on fragility; It was stated that 50.9% of them think of the most vulnerable and weak patient when they think of a fragile patient. While 50% of them stated that when they suspected frailty in the patient, they evaluated involuntary weight loss, slowness (slowness in walking, muscle weakness), and fatigue; 70% stated that the biggest risk factor for frailty is being depressed or using antidepressant medication.
Conclusions: According to the results of the study, it can be said that the awareness of surgical nurses about the "fragile patient" should be increased. In the light of the data obtained, it can be suggested to organize trainings on "fragile patients" for surgical nurses. 'Fragile patient' education should be included in pre-graduation education and in-service training.
Keywords: Fragility, surgical nursing, fragile patient, awareness

*T*he average human lifespan is increasing due to the increase in the quality of medical care in parallel with technological developments around the world [1]. According to the estimates of the World Health Organization, the number of people aged 60 and over is expected to reach two billion people in 2050, and the majority of this population is expected to be in the middle and lower income group [2]. Increasing elderly population brings with it increasing health expenditures, the need for infrastructure regulation and problems. The adaptation process to the increasing elderly population is challenging, especially for economically underdeveloped and developing countries, and it is of great importance to identify the

problems correctly and produce solutions quickly and feasibly [3].

With the aging of the population, the concept of 'fragility' gains importance. 'Fragility', also referred to as fragility, is a condition that negatively affects life satisfaction [4, 5]. Frailty is a syndrome that can occur in a wide range of areas, from mild physical inactivity to immobility, in patients over the age of 65, and can also affect cognitive disorders at certain levels [6]. General symptoms; slowness in walking, unconscious weight loss, decrease in appetite, decrease in Body Mass Index (BMI), gradual loss of muscle strength, feeling of inadequacy when performing physical movements, weakness, fatigue, deterioration in cognitive functions and memory loss [7].

Surgical patients are physically and psychologically vulnerable due to perioperative stress. This sensitivity accompanied by frailty syndrome can further increase the negative effects of the perioperative process in elderly patients. It is thought that evaluation of preoperative and postoperative frailty in surgical patients will provide useful additional information about postoperative morbidity, mortality, prognostic status and discharge [8].

In the care of fragile elderly people, the nurse, together with the healthcare team, should be able to detect complications that may develop in the elderly at an early stage, take the necessary precautions and provide treatment or rehabilitation services as needed [9]. For this reason, it is recommended that nurses have knowledge about frail elderly characteristics, frailty symptoms and risk factors [10].

It has been evaluated that surgical nurses' awareness of the fragility of patients, their awareness of this syndrome, and planning nursing care for fragile patients can contribute positively to the recovery of these patients. No study has been found in Turkey investigating the vulnerability awareness of surgical nurses in patients. In addition to determining the knowledge of surgicaL nurses about frailty and creating awareness on this issue; this study was planned with the idea that it could form a basis for future studies and that the data obtained could be used in planning the education of nurses.

In this study, it was aimed to determine the awareness of nurses working in surgical clinics about the frailty of elderly or adult surgical patients and their awareness of frail patients.

METHODS

Population and Sample of the Research

This research is a descriptive and cross-sectional study conducted to determine surgical nurses' recognition and awareness of fragile patients. The research was conducted in the surgical services of a public hospital in Turkey between September and October 2022. The universe of the research; There were 150 nurses working in surgical services. Nurses who have been actively working for at least one year in surgical clinics who voluntarily agreed to participate in the study. In the study, it was aimed to reach the whole universe. Before starting the research, Ethics Committee approval (dated 14.06.2022 and no: 2022-042) and institutional permission were obtained from the institution where the research will be conducted. During the data collection process, the researcher (İÖ) first visited the surgery clinics and gave verbal and written information about the research and distributed the survey forms to the volunteer nurses to participate in the study. After approximately 30 minutes, he visited the clinics and collected the forms again. 110 nurses participated in the study voluntarily and filled out the data collection forms completely and gave them to the researcher. In order to determine the adequacy of the sample size, it was determined that the sample number should be at least 54 in the sample calculation made with 0.5 effect size, 95% power and 0.05 margin of error using the G*Power 3.1.9.7 (Franz Faul, Universitat Kiel, Germany) program. In this case, since 110 nurses participated in the study, it was concluded that sufficient sampling was achieved. Of the 40 nurses who were not included in the study, 28 did not agree to participate in the study, and 12 were determined to be nurses who were not actively working at the time the study was conducted.

Data Collection Forms

In order to obtain the data of the study, the "Introductory Information Survey Form" created by the researchers and the "Fragile Patient Information Evaluation Form" created based on the literature [11, 12] were used.

Introductory Information Survey Form

Descriptive characteristics of nurses (age, education level, years of experience in the profession, the

Table 1. Distribution of surgical nurses according to their descriptive characteristics (n=110)

Introductory features	Mean±SD	Min.-Max.
Age (year)	28±5.01	22-46
Duration of Professional Experience (years)	5±5.09	1-28
Duration of working in the service you work in (years)	3 ±2.83	1-19
	n	**%**
Age group (years)		
20-26 years	40	36.4
26-32 years	46	41.8
32-46 years	24	21.8
Educational status		
Health vocational high school + associate degree	13	11.8
License and Above	97	88.2
Job description in the service you work for		
Service/clinic nurse	95	86.4
Training nurse	1	0.9
Service responsible nurse	4	3.6
Intensive care nurse	10	9.1
How to work in the service you work for		
Daytime shift only (08.00-16.00)	17	15.5
Day shift + Seizure	41	37.3
Variable shift (alternating triple shift system)	11	10
Fixed shift (in a fixed shift segment on a triple shift)	3	2.7
Night shift only (16.00-24.00 or 24.00-08.00)	38	33.5

length of time you have worked in the ward you work in, your job description in the ward you work in, the way you work in the ward you work in), the status of receiving training on frail patients, the first expression that comes to mind when talking about frail patients, what do you evaluate when you suspect frailty in a patient? , what are the risk factors for frailty, do you evaluate the patients you care for in terms of frailty, do you prepare a care plan for the frail patient when you detect a frail patient, what is the impact of the frail patient on the hospital cost in surgical clinics, do you consider the concept of frailty as a risk factor for the surgical patient, Is being a frail patient an independent risk factor for hospital stay and delayed discharge? Have you used a frail patient scale in the ward you work in? Do you feel competent in the nursing management of frail patients? Is frailty seen only in elderly patients? Have you heard the terms physical frailty and cognitive frailty before? A 21-question survey form was used, which included questions such as "When you identify a fragile patient, would you share this information with your teammates?" and "Is multidisciplinary care and treatment necessary for a fragile patient?"

Statistical Analysis

The research data were transferred to the SPSS for Windows V-23.0 program and number (n), percentage (%), mean ±standard deviation values were calculated as descriptive statistics.

RESULTS

The distribution of the nurses participating in the study according to their descriptive characteristics is given

in the table. According to this; the average age of nurses is 28±5.01 years, their average professional experience is 5±5.09 years, and their average experience in the ward they work in is 3±2.83 years. While 41.8% of the nurses participating in the study were between the ages of 26-32; 88.2% had a bachelor's degree or above; The job description in the ward where 86.4% worked was ward/clinic nurse; It was determined that the working style of 37.3% of them was Day + duty (Table 1).

It was stated that 92.7% of the 110 surgical nurses participating in the study did not receive any training on fragility; It was stated that 50.9% of the patients, the most vulnerable and weak patient comes to mind first when the fragile patient is mentioned. When they suspect frailty in a patient, 50% of them state that they evaluate involuntary weight loss, slowness (slowness in walking speed, muscle weakness), and weakness; 70% stated that frailty is the biggest risk factor being depressed or using antidepressant medication (Table 2).

Table 3 shows the distribution (n=110) of the answers given to the questions asked to the nurses about the 'fragile patient'. According to the Table, the nurses

Table 2. Distribution of nurses according to their answers, what they evaluate when they suspect, the first thing that comes to mind when they think of 'fragile patient' education and vulnerability

	n	%
1. Have you received any training about the fragile patient?		
Yes	8	7.3
No	102	92.7
2. What is the first phrase that comes to your mind when you say frail patient?		
The most vulnerable and weakest patient	56	50.9
Patients who are stressed and at increased risk of becoming stressed	40	36.4
Patient with low physical activity	9	8.2
Tired patient	1	0.9
weak patient	2	1.8
Patient with weight loss	2	1.8
3. Which ones do you evaluate when you suspect frailty in a patient?		
Involuntary weight loss	6	5.5
Slow movement	19	17.3
Exhaustion	7	6.4
All	55	50
None	4	3.6
No idea	19	17.3
4. Which of the following is among the risk factors for frailty*?		
Advanced age	48	43.6
Low level of education	27	24.5
Continuing smoking and alcohol consumption in old age	26	23.6
Being on hormone therapy after menopause	21	19.1
Be operated	28	25.5
Not being married	12	10.9
Being depressed or taking antidepressant medication	78	70.9

*This is the answer of 110 people, it has been multiplied by n since more than one option can be marked.

Table 3. Distribution of the answers given to the questions asked to the nurses about the 'fragile patient' (n=110)

QUESTIONS	Yes	No	I am not aware of such a concept
	n (%)	n (%)	n (%)
1. When planning treatment and care for a fragile patient, is it important to provide treatment and care to the individual and her family with a holistic approach?	100 (90.9)	10 (9.1)	0
2. When you identify the fragile patient, would you share it with your teammates?	53 (48.2)	12 (10.9)	45 (40.9)
3. Is multidisciplinary care and treatment necessary for a fragile patient?	53 (48.2)	3 (2.7)	54 (49.1)
4. Is being a frail patient an independent risk factor for hospital stay and delayed discharge?	53 (48.2)	12 (10.9)	45 (40.9)
5. Do you consider the concept of frailty as a risk factor for the surgical patient?	52 (47.3)	11 (10.0)	47 (42.7)
6. Do you assess the patients you care for frailty?	31 (28.2)	61 (55.4)	18 (16.4)
7. Do frail patients increase hospital costs in surgical clinics?	31 (28.2)	16 (14.5)	63 (57.3)
8. Have you heard the terms physical frailty and cognitive frailty before?	24 (21.8)	86 (78.2)	0
9. When you detect a frail patient, do you prepare a care plan for the frail patient?	20 (18.2)	38 (34.5)	52 (47.3)
10. Do you feel competent in fragile patient management?	11 (10)	43 (39.1)	56 (50.9)
11. Have you used a frail patient scale in the service you work in?	3 (2.7)	107 (97.3)	0
12. Is the fragile patient seen only in geriatric patients?	2 (1.8)	48 (43.6)	60 (54.5)

were asked to answer the questions asked as yes, no and I am not aware of such a concept. The answers given are combined and given in Table 3. Do you assess the patients you care for frailty? While 61% answered no to the question; 52% when you detect a frail patient, do you prepare a care plan for the frail patient? He answered the question, "I am not aware of such a concept." 63%: Do frail patients increase hospital costs in surgical clinics? He answered his question as "I am not aware of such a concept."

DISCUSSION

Frailty in the patient can be listed as slowness in walking, weight loss, decrease in appetite, decrease in body mass index, weakness and fatigue due to decrease in muscle strength, and deterioration in cognitive functions [12]. Frailty is also defined as the disorder of several interrelated physiological systems [11].

Distinguishing frail from non-frail older persons should be an essential part of the assessment in any healthcare encounter that may or may potentially result in an invasive procedure; harmful medicine allows doctors to weigh benefits, risks, and patients to make informed choices. The potential failure to detect frailty exposes patients to interventions from which they may not benefit and may actually be harmed [12].

In a study conducted by Çakmur *et al.* [13] in rural areas of Kars, the frailty level in individuals over the age of 65 was determined as 7.1%, while the pre-frailty period rate was determined as 47.3%. In their

study by O'Caoimh *et al*. [14] it was determined that the lowest overall frailty rate in Europe over the age of 65 was 3.7% (Norway); the highest rate was determined as 41.5% (Ireland). In Turkey, these values were determined to be mildly frail, 10% moderately frail, and 13.1% severely frail, among individuals over the age of 65[15].

In the study conducted by Akturan *et al*. [11] the frailty survey form was applied to 58 family physicians, and the rate of those who answered correctly to the question of the first word that comes to mind when 'Fragility' was mentioned was 12.1%. In the same study, 38.2% answered yes to the question whether they evaluated patients in terms of frailty; In this study applied to family physicians, 5.2% of physicians stated that they had no idea what to do when they suspected frailty. In our study, it was stated in the survey applied to nurses that 50.9% of them said that when they say fragile patient, the first thing that comes to mind is the most vulnerable and weak patient; In the study, 39% of the nurses surveyed answered yes to the question of whether they evaluate patients for frailty; 17.3% of nurses stated that they had no idea what to do when they suspected frailty. Looking at these data, while our study and the study conducted by Akturan determined similar values in terms of evaluating the patient in terms of frailty, it was determined that the rate of nurses not knowing what to do when a frail patient is suspected was higher. Additionally, looking at the data of our study, the fact that only 10% of nurses feel competent in managing fragile patients' reveals the gravity of the situation.

When we make a general evaluation of the results of our study, the most striking finding is that the majority of nurses have insufficient awareness of the 'frail patient'. In addition, the fact that 92.7% of 110 surgical nurses stated that they did not receive any training on frailty reveals the lack of education. This situation also creates a deficiency in understanding the importance of the multidisciplinary approach, the treatment and care of frail patients, and its relationship with hospital stay and cost.

Although there are many studies on frail patients in the literature, there are no studies that measure nurses' frailty knowledge and experience levels. For this reason, it is anticipated that this study will be the source of many studies.

CONCLUSION

Our study provides insight into how surgical nurses conceptualize the frail patient. Additionally, it was revealed that surgical nurses' level of knowledge about frailty patients was not sufficient. In the light of the data obtained, it can be said that in-service training on 'frail patient' and 'frailty patient assessment' should be organized for surgical nurses and that these trainings should be increased. There is a need for comprehensive, multicenter studies on the awareness, knowledge levels and practices of primary healthcare professionals about 'frail patients'.

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Distribution of neuropsychiatric profiles and comorbid diseases in dementia subtypes

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ABSTRACT

Objectives: Alzheimer's disease (AH) is the most prevalent cause of dementia, followed closely by vascular dementia. Mixed vascular-Alzheimer's dementia (MVAD) is more evident in individuals aged 80 and above. Frontotemporal dementia (FTD) is the second most common cause of early-onset dementia after AH. Vascular risk factors play important role in the pathogenesis of dementia syndromes. Behavioral and psychological symptoms represent a significant portion of the non-cognitive manifestations in dementia patients. This study aimed to evaluate the distribution of chronic diseases, behavioral disorders, psychiatric findings, and medication use in patients followed with different dementia diagnoses.

Methods: Prevalance of chronic diseases, behavioral disorders, psychiatric findings as well as the usage of antidepressant and antipsychotic medications among patients followed up in dementia outpatient clinics with the diagnosis of AD, mild cognitive impairment (MCI), vascular dementia (VaD), FTD, and MVAD were investigated. Neuropsychiatric inventory (NPI) was applied to the patients.

Results: Four hundred and fifty-five patients were accepted in the study. The patients were distributed as follows: AD (n=303, female/male: 187/115, age = 78±8 years), MCI (n=53, female/male: 31/22, age = 69±10 years), VaD (n=31, female/male: 18/13, age = 68±9 years), FTD (n=32, female/male: 17/15, age = 68±9 years), and MVAD (n=36, female/male: 16/20, age = 76±10 years). Both AD and MVAD groups were significantly older than the other groups (F = 23.2, P<0.0001). The ratio of comorbid chronic diseases was 80% in the AD group, 72% in the MCI group, 91% in the VaD group, 59% in the FTD group, and 93% in the MVAD group. In the whole group, antipsychotic drug use was 27.5% and antidepressant drug use was 28.9%. The mean NPI

score was 32.9±28 in antipsychotic users and 16±19 in non-users (P<0.0001). The mean NPI of antidepressant users was 17.6±19 and 21.9±25 (P=0.055) in non-users.
Conclusion: There is a comorbid chronic disease burden in all dementia subtypes, although at varying intensities, and as the chronic disease burden increases, behavioral disorders and psychotic findings increase, and accordingly, the use of antipsychotics also increases.
Keywords: Dementia, chronic disease, behavioral disorders, antidepressants, antipsychotic

*D*ementia is a rapidly growing global health concern, particularly affecting individuals aged 65 and older. Alzheimer's disease (AD) stands as the most prevalent cause of dementia, followed closely by vascular dementia (VaD) [1]. Notably, the occurrence of mixed vascular-Alzheimer's dementia (MVAD) has exhibited a rising trend, becoming more evident in individuals aged 80 and above, with prevalence climbing from an average of 25% to 35%. The autopsies performed on individuals over the age of 85 with mixed vascular-Alzheimer's dementia have revealed distinctive brain changes characterized by astrogliopathy, synucleinopathy, and TDP43 protein aggregation [2]. Frontotemporal dementia (FTD) emerges as the second most common cause of early-onset dementia in individuals under the age of 65, ranking just behind AD [3]. Recent research indicates to the active role of vascular risk factors in various types of dementia, suggesting that most forms of dementia can be viewed as integral components of vascular disease [4].

Behavioral and psychological symptoms represent a significant portion of the non-cognitive manifestations in dementia patients. These symptoms not only contribute to heightened morbidity and burden on the caregivers but also lead to a decline in the quality of life for both the affected patient and their caregiver [5]. The spectrum of behavioral disorders associated with dementia includes anxiety, depression, irritability, psychomotor agitation, delusions, hallucinations, apathy, disinhibition, abnormal motor behaviors, and circadian rhythm disorders. The intensity and expression of these symptoms and disorders exhibit heterogeneity among patients and may vary over time. The presence of specific behavioral disorders within distinct subtypes of dementia remains a subject of debate in the field [5].

In our previous study, we investigated the neuropsychiatric effects of total and partial lockdown measures in 302 Alzheimer's patients who were followed up during the COVID-19 pandemic [6]. As a continuation of that study, this time we investigated the follow-up of dementia patients, the burden of comorbid chronic diseases, the distribution of behavioral and psychotic disorders, and the intensity of antidepressant and antipsychotic medication use by including other types of dementia as well as AD.

METHODS

This study involves a further follow-up of patients, who were followed in a multicenter study titled "Neuropsychiatric Effects of COVID-19 Pandemic on Alzheimer's Disease: A Comparative Study of Total and Partial Lockdown" [6] and is its continuation. The diagnoses are based on the criteria defined by DSM-IV (Diagnostic and statistical manual of mental disorders) and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) for Alzheimer's Disease (AD), NINDS-AIREN (National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences) [7] for Vascular Dementia (VaD), and Petersen for mild cognitive impairment (MCI) [8].

All FTD patients were behavioral variants and were diagnosed according to the diagnostic criteria proposed by Rascovsky *et al*. [9]. MVAD was diagnosed according to the criteria of Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC). Even though MVAD is very similar to Alzheimer's disease, which is a primary amnestic syndrome, the cranial imaging shows cerebral vascular changes (leukoaraiosis, diffused white matter changes, lacunes) along with cognitive disorders [10].

The chronic diseases included in the study were hypertension, DM, chronic heart disease, chronic kidney disease, stroke, hypothyroidism, and cancer. For

chronic heart diseases, coronary heart disease and heart failure were included.

Neuropsychiatric inventory (NPI) was applied to the patients [11]. In addition, the total scores were considered for depression, anxiety, irritability, and agitation as neurotic symptoms; hallucinations and delusions as psychotic symptoms; and sleep and eating disorders as circadian rhythm disorders in the NPI. For the last category, apathy, euphoria, disinhibition and abnormal motor behaviors were considered in the total score of others [5]. The severity of dementia was assessed on the CDR (Clinical Dementia Rating) scale [12].

Statistical Analysis

For statistical analyses, SPSS version 16.0 (IBM, Chicago, IL, USA) was used. Demographic data was expressed as mean ± standard deviation and categorical data as percentage (%). A two-way ANOVA was used to analyze multiple groups, Pearson's correlation coefficient for correlation analysis, and Student's t-test for comparing the averages of two groups. LSD was used as post-hoc analysis in the ANOVA test. Multiple regression analysis was performed to determine the factors affecting NPI. Statistical significance value was accepted as $P<0.05$.

RESULTS

This study involved a further follow-up of dementia patients, who were followed after the COVID-19 pandemic in the previous study, as well as an investigation of the burden of comorbid chronic diseases, the distribution of behavioral and psychotic disorders, and the intensity of antidepressant and antipsychotic medication use.

This multicenter, cross-sectional study included 488 patients. After excluding 33 patients due to Parkinson's disease, dementia with Lewy bodies, normal pressure hydrocephalus, and Parkinson's disease dementia, 455 patients remained in the study. The patients were distributed as follows: AD (n=303, female/male: 187/115, age = 78±8 years), MCI (n=53, female/male: 31/22, age = 69±10 years), VaD (n=31, female/male: 18/13, age = 68±9 years), FTD (n=32, female/male: 17/15, age = 68±9 years), and MVAD (n=36, female/male: 16/20, age = 76±10 years). On average, both AD and MVAD groups were significantly older than the other groups (F = 23.2, P<0.0001). There was no statistically significant difference between the groups in terms of gender (F = 0.97, P=0.41). There was no statistically significant difference between the groups in terms of education level (F = 0.91, P=0.45).

In our study, 68% of the entire dementia group had hypertension, 24% had DM, 15% stroke, 28% heart disease, 1% cancer, 3% renal failure, and 2% hypothyroidism. The ratio of comorbid chronic diseases was 80% in the AD group, 72% in the MCI group, 91% in the VaD group, 59% in the FTD group, and 93% in the MVAD group. The lowest ratio of comorbid chronic

Table 1. Distribution of chronic diseases by different types of dementia

	AD	MCI	VaD	FTD	MVAD	F	Pvalue
Hypertension	68%	57%	78%	55%	79%	1.38	0.23
DM	24%	17%	30%	14%	39%	1.72	0.14
Heart failure	31%	13%	30%	23%	32%	1.91	0.10
Kidney failure	2%[a]	6%[a]	0%[a]	0%[a]	11%[b]	2.55	**0.03**
Stroke	9%[a]	4%[a]	78%[b]	9%[a]	57%[c]	43.4	**<0.0001**
Cancer	1%	2%	0%	0%	0%	0.28	0.88
COPD	5%	4%	4%	0%	4%	0.28	0.88
Hypothyroidism	3%	0%	0%	0%	4%	0.7	0.59

AD=Alzheimer's disease, MCI=Mild cognitive impairment, VaD=Vascular dementia, FTD=Frontotemporal dementia, MVAD=Mixed vascular-Alzheimer's dementia, DM=diabetes mellitus, COPD=chronic obstructive pulmonary disease, [a]-[c]There is no difference between groups with the same letter for each measure.

Table 2. Distribution of behavioral and psychiatric symptoms and medication use in different types of dementia

	AD	MCI	VaD	FTD	MVAD	F	P value
Antipsychotics	31%[a]	0%[b]	30%[a]	32%[a]	32%[a]	5.99	**<0.0001**
Antidepressants	26%[a]	26%[a]	44%[a,c]	32%[a,c]	50%[b,c]	2.49	**0.04**
Cholinesterase inhibitors	82%[a]	55%[b,c]	44%[b]	32%[b,c]	75%[a]	13.1	**<0.0001**
Glutamate antagonists	43%[a]	6%[b]	17%[b,c]	27%[a,b,c]	32%[a,c]	8.37	**<0.0001**
NPI	22±24[a]	6±7[b]	19±24[a]	25±25[a]	22±24[a]	6.17	**<0.0001**
Neurotic symptoms	6.8±8[a]	3.2±4[b]	7.8±10[a]	8.6±11[a]	8.2±9[a]	2.97	**0.01**
Psychotic symptoms	3.8±5[a]	0.3±0.7[b]	3.6±6[a]	3.7±6[a]	5.2±6[a]	6.5	**<0.0001**
Circadian rhythm disorders	4.9±6[a]	1.6±3[b]	4.6±7[a,b]	4.9±5[a]	4.3±6[a,b]	2.64	**0.03**
Others	3.3±5[a]	0.2±0.6[b]	2.7±3[a]	6.3±5[c]	3.7±6[a]	6.9	**<0.0001**
NPI							
Antipsychotics (+)	32.6±28	-	46.2±29	18±16	37.8±27		
Antipsychotics (-)	18.3±20	6.1±7	8.1±9	28.2±29	15.8±19		
P value	**<0.0001**		**0.01**	0.39	**0.02**		
NPI							
Antidepressants (+)	19.4±18	9.6±10	13.6±24	27.4±34	13.2±11		
Antidepressants (-)	23.9±25	4.8±6	24.5±24	23.8±21	32.5±30		
P value	0.09	**0.04**	0.3	0.7	**0.04**		

AD=Alzheimer's disease, MCI=Mild cognitive impairment, VaD=Vascular dementia, FTD=Frontotemporal dementia, MVAD=Mixed vascular-Alzheimer's dementia, DM=diabetes mellitus, COPD=chronic obstructive pulmonary disease, NPI=neuropsychiatric inventory. Antipsychotics (+)=using antipsychotics, Antipsychotics (-)=not using; Antidepressants (+)=using antidepressants, Antidepressants (-)=not using. [a-d]There is no difference between groups with the same letter for each measure.

Table 3. Distribution of behavioral and psychiatric symptoms and ratios of medication use depending on the severity of dementia

CDR	0.5	1	2	3	F	P
N	149	171	83	52		
Antipsychotics	11%[a]	34%[b]	37%[b]	43%[b]	5.99	**<0.0001**
Antidepressants	34%	27%	22%	29%	2.49	0.33
Cholinesterase inhibitors	66%	76%	78%	77%	1.95	0.12
Glutamate antagonists	17%[a]	33%[b]	59%[c]	61%[c,d]	20.0	**<0.0001**
NPI	8±1[a]	22±25[b]	26±23[b]	44±25[c]	35.6	**<0.0001**
Neurotic symptoms	4±5[a]	7.9±9[b]	7.1±8[b]	9.6±8[b]	7.94	**<0.0001**
Psychotic symptoms	0.8±1[a]	3.8±5[b]	5.2±5[c]	7.7±5[d]	31.2	**<0.0001**
Circadian rhythm disorders	1.9±3[a]	4.6±5[b]	5.8±6[b]	11.4±8[c]	24.8	**<0.0001**
Others	0.9±2[a]	3.5±6[b]	4.5±5[b,c]	5.7±5[c]	15.6	**<0.0001**

CDR=clinical dementia rating scale, NPI=neuropsychiatric inventory, [a-d]There is no difference between groups with the same letter for each measure.

Table 4. Correlation analysis between age and NPI scores in dementia types

	AD	MCI	VaD	FTD	MVAD
NPI/ Age	0.177	0.109	0.210	0.157	0.549
P value	**0.002**	0.43	0.33	0.48	**0.002**

NPI=neuropsychiatric inventory, AD=Alzheimer's disease, MCI=Mild cognitive impairment, VaD= Vascular dementia, FTD=Frontotemporal dementia, MVAD= Mixed Vascular-Alzheimer's Dementia

disease was in the FTD group (F = 3.19, P=0.01). When the distribution of chronic diseases in different types of dementia is examined, stroke in the VaD group and renal failure in the MVAD group were found to have a significantly higher rate than the other groups. (Table 1).

The numbers of chronic diseases were identified as 1.4±1 in AD, 1±0.8 in MCI, 2.2±1 in VaD, 1±1 in FTD, and 2±1 in the MVAD groups. A comparison of both VaD and MVAD groups with the other groups showed a statistically significant difference in the number of chronic diseases (F = 10.3, P<0.0001). In the whole group, antipsychotic drug use was 27.5% and antidepressant drug use was 28.9%. The mean NPI score was 32.9±28 in antipsychotic users and 16±19 in non-users (P<0.0001). The mean NPI of antidepressant users was 17.6±19 and 21.9±25 (P=0.055) in non-users. Table 2 shows the distribution of drug use and NPI symptoms in different types of dementia. There is no use of antipsychotics in MCI, but they are

used in around 30% of other types of dementia. Antidepressant medications are most used in the MVAD type. This is followed by VaD and FTD dementia. No significant difference was detected between dementia types in posthoc analyses. Cholinesterase inhibitors are used most in AD and MVAD type dementia and least in FTD. Glutamate antagonists are least used in MCI. Average NPI scores are highest in FTD type and lowest in MCI type. Neurotic and psychotic symptoms, circadian rhythm disorders and other NPI symptoms were found to be significantly lower in MCI than in other dementia types (Table 2). In other types of dementia, except for FTD, NPI scores are higher in those who use antipsychotics than in those who do not use antipsychotics drugs. In the MCI and FTD groups, NPI scores of those using antidepressants were higher (Table 2).

The mean NPI score of patients with chronic diseases was 21.7±24 and 16.5±20 (P=0.06) in patients without chronic diseases. There was a positive corre-

Table 5. Regression analysis results of factors affecting NPI

	B	SD	β	P value
NPI	99.88	33.8		
Age	0.25	0.11	0.1	**0.028**
CDR	11.49	1.35	0.38	**0.0001**
Hypertension	1.73	2.32	0.033	0.45
Diabetes mellitus	-3.06	2.45	-0.055	0.21
Heart failure	-4.32	2.38	-0.082	0.07
Kidney failure	-9.54	6.30	-0.067	0.13
Stroke	-5.93	2.96	-0.089	**0.046**
Cancer	-20.51	9.54	-0.093	**0.032**
COMD	-11.69	5.14	-0.099	**0.023**
Hypothyroidism	-3.01	7.18	-0.018	0.67

SD=standard deviation, B=Unstandardized coefficient β=Standardized coefficient, CDR=Clinical Dementia Rating, NPI=neuropsychiatric inventory. Dependent variable: NPI R2=0.232

lation between the ages and NPI scores of the patients (r= 0.236, P<0.0001). Accordingly, as the number of chronic diseases increased, so did the NPI score (r= 0.143, P=0.003). A positive correlation was found between NPI score and CDR (r= 0.420, P<0.0001). In Table 3, antipsychotic use is lowest in the dementia group with CDR 0.5, and glutamate use is highest in the group with CDR 2 and 3. The highest NPI scores and subsections are in the group with CDR 3. In the correlation analysis of age and NPI in dementia types, a positive significant correlation was detected only in AD and MVAD type dementia (Table 4). In the regression analysis, the most effective parameters on NPI were determined to be age, CDR, stroke, cancer and COPD (Table 5).

DISCUSSION

This study focused on the distribution of chronic diseases, behavioral disorders, psychiatric findings and the prevalence of antipsychotic and antidepressant drug use in patients followed in dementia outpatient clinics with different dementia diagnoses.

It is reported that the burden of chronic disease is high in elderly individuals with dementia, with stroke found in 24% and coronary artery disease in 33%. Hypertension is a major risk factor for the brain, while depression, DM and coronary heart diseases have been reported to be more important factors in developing memory defects [13]. In our study, the highest rates of comorbid diseases were hypertension, heart diseases, diabetes mellitus and stroke. In terms of dementia types, the comorbid disease burden is found in MVAD, VaD, AD, MCI and FTD, respectively. Hypertension, heart failure, and DM were found to be at the highest ratios in the VaD and MVAD groups. A comparison among dementia types has shown that stroke was significantly higher in VaD and MVAD, while renal failure was significantly higher in MVAD. The prevalence of cognitive dysfunction in chronic kidney diseases has been reported as 16-38% [14]. It is suggested that this condition is caused by the accumulation of various endogenous and exogenous substances in the blood that are toxic to the brain, disruption of the blood-brain barrier, systemic inflammation, activation of NMDA receptors and oxidative

stress [14]. In uremic animal models, pyknosis and apoptosis have been demonstrated in hippocampal neurons. Widespread white matter changes have been shown in 33% of patients with chronic renal failure, and these have been stated to cause cognitive effects [15]. In our study, a high rate of renal failure was detected in the MVAD group. The higher rate of kidney failure in the MVAD group than the other dementia groups may suggest more severe vascular involvement as well as the hippocampus.

Seventy percent of stroke survivors develop cognitive deficits depending on the type of stroke and level of disability. This may occur in patients with subarachnoid, intracerebral hemorrhages and ischemic stroke [16, 17].

Typically, cognitive deficits are known to appear 3-6 months after a stroke; however, some researchers define these as early- and late-onset cognitive deficits [18]. Irreversible cognitive impairments that appear within six months after a stroke are called "post-stroke dementia" [19]. No distinction is made between vascular cognitive impairment and post-stroke cognitive impairment, which are both addressed within the scope of vascular dementia [18]. Furthermore, risk factors such as hypertension, heart diseases and DM play a major role in vascular dementia [20]. According to the CogFAST study, the presence of three or more cardiovascular risk factors at advanced ages increases the risk of post-stroke dementia by 3.6 [21]. In our study, stroke was detected at a rate of 78% in VaD type dementia and 57% in MAVD type dementia. The number of chronic diseases is two or more in these two groups of dementia. AD and MVAD type dementias are seen at an older age than other dementias.

Some studies have suggested that the dementia subtypes do not present differences in terms of behavioral and psychological symptoms. The intensity of neuropsychiatric symptoms in dementia subtypes may fluctuate over time, and several factors, including various underlying neurobiological changes, comorbidities, pathologies in cerebral vascularization, and age play a role in such fluctuations [22]. In addition to cognitive loss, Alzheimer's disease also presents symptoms such as behavioral changes, psychosis, mood swings, apathy, agitation, and abnormal motor behaviors [23]. Patients with vascular dementia demonstrate a specific neuropsychiatric pattern characterized by

depression with low response to antidepressants, as well as psychomotor decline, anxiety, apathy, and emotional withdrawal [10, 24].

In the behavioral variant of frontotemporal dementia, symptoms such as personality changes, disinhibition, inappropriate sexual behavior, and socially maladaptive behaviors are observed predominantly [25]. While disinhibition is the most prominent symptom, apathy is also a common early finding that may present in the form of loss of interest in social and non-social activities. Excessive alcohol intake and smoking, excessive consumption of sweets, hyperorality, and inappropriate behaviors may also be noted. FTD patients with C9ORF72 mutation may present psychotic symptoms such as visual and auditory hallucinations and delusions [26].

In our study, symptoms, including neurosis, psychosis, circadian rhythm disorders, and other behavioral disorders were observed in the lowest rates in the MCI group. Among these, neurosis and other behavioral disorders were the highest in FTD, psychotic behaviors the highest in MVAD, and circadian rhythm disorders the highest in AD and FTD groups. In terms of rating dementia, all behavioral disorders increased as did the CDR score. In our study group, behavioral disorders increased in direct correlation to the increase in age and chronic disease burden. An increase in neuropsychiatric symptoms with age has been observed, especially in AD and MVAD type dementias. In the regression analysis, age, CDR, stroke, cancer and COPD were determined as effective factors in neuropsychiatric symptoms.

The types and severity of psychiatric symptoms may vary throughout the course of dementia. Morbidity in patients leads to poorer quality of life, thus increasing the caregivers' burden [27].

Even though antipsychotics have side effects such as worsening morbidity and disability, they are still used to treat behavioral disorders in the natural course of dementia. Other undesirable side effects include decline in cognitive performance, falls, delirium, hypotension, and sedation as well as extrapyramidal side effects. In contrast, atypical antipsychotics tend to be safer and more tolerable medications [28].
A study conducted in 2015 in the UK reported that fewer than 50% of patients with dementia used antipsychotics [29]. It was further reported that 20% of dementia patients were prescribed antipsychotics to treat symptoms such as agitation, aggression, yelling, sleep disorders, behavioral symptoms, hallucinations, and delusions, with only one fourth of the patients benefiting from these medications [30]. In our study, approximately 30% of all dementia subtypes except for the MCI group were prescribed antipsychotics. When evaluated in terms of antipsychotics, NPI scores were found to be high in those using antipsychotics in the AD, VaD and MVAD groups. In the FTD group, NPI scores were higher in patients not using antipsychotics. We can explain this situation by being selective in the use of antipsychotics in dementia patients and mostly giving them to the patients with significant behavioral disorders and psychotic symptoms. We can attribute the higher NPI scores of FTD patients who do not use medication to the fact that the patients are non-compliant with treatment and their control is more difficult.

The effectiveness of antidepressants is also a highly debated topic. Some researchers defend that a positive response is achieved, while others argue that they are ineffective [31]. The effective dose range also varies [32]. Moreover, antidepressants may lead to increased risk of falls, higher mortality, and hospitalization in this age group [33]. Selective serotonin reuptake inhibitors (SSRIs) are the most common antidepressant group prescribed for these patients [34]. In our study group, antidepressants were used by 44% and 50% of the VAD and MVAD groups, respectively, 26% of the AD and MCI groups, and 32% of the FTD group. NPI scores were found to be higher in the AD, VaD and MVAD groups that did not use antidepressant medication. In the MCI and FTD groups, NPI scores were higher in those using antidepressant medication. We can explain this situation by the fact that antidepressant drugs are used less than necessary in the AD, VaD and MVAD groups.

In recent years, exercise therapy, light therapy, music therapy, and massage therapy are also recommended as non-pharmacologic approaches [35].

Limitations

The limitations of our study were the limited number of cases and the non-availability of individual depression and anxiety scales. Further studies are recommended by increasing the number of patients,

assessing the response to antidepressant and antipsychotic treatments, and evaluating the side effect profiles.

CONCLUSION

In conclusion, all dementia subtypes come with a comorbid chronic disease burden in varying intensities, and behavioral disorders and psychotic findings increase as does the chronic disease burden. While the behavioral disorders and psychiatric symptoms coexisting with dementia types do not present a very specific pattern, depression, anxiety, irritability, and agitation were observed prominently in FTD and MVAD; the circadian rhythm disorders, which include sleep and eating disorders, were observed significantly in AD and FTD; hallucinations and delusions were seen in MVAD; and apathy, euphoria, disinhibition, and abnormal motor behaviors, included in others, were noted significantly in FTD. Even though antipsychotics were prescribed for 30% of all dementia subtypes, except for FTD, antidepressants were used more intensively, particularly in VAD and MVAD. It has been observed that age, CDR and chronic diseases, especially stroke, cancer and chronic obstructive pulmonary diseases, are effective on neuropsychiatric findings. Detection and effective treatment of chronic diseases are at least as important as medications in controlling neuropsychiatric findings and should be handled carefully.

Ethics Committee Approval
This study was approved by the clinical research ethics committee of Maltepe University Faculty of Medicine Ethics Committee Date: (2020/900/54).

Authors' Contribution
Study Conception: SK, NGB; Study Design: SK, NGB; Supervision: SK; Funding: N/A; Materials: N/A; Data Collection and/or Processing: SK, NGB, NÇ, MFA, ŞŞ, FSK, ÖGÖ, TO, FE, DYO, ÖT, MKG, EAD, ZY, HE, BSAP, NE, EKT, ÖA; Statistical Analysis and/or Data Interpretation: SK, ŞŞ; Literature Review: SK, NGB; Manuscript Preparation: SK, NGB and Critical Review: ŞŞ, SK, NÇ.

Conflict of interest
The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evolving paradigms in the diagnosis and management of premenopausal women with abnormal uterine bleeding

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ABSTRACT

Abnormal uterine bleeding (AUB) is a common gynecological complaint among premenopausal women, encompassing a wide range of underlying disorders that complicate diagnosis and management. The evolving paradigms in medical science now incorporate advanced imaging techniques, personalized medicine, and molecular diagnostics to improve the accuracy of diagnoses and the effectiveness of treatment plans. This review examines recent advancements in the diagnostic approach, including the use of transvaginal ultrasonography, hysteroscopy, and biomarker analysis, which have significantly refined the identification of endometrial pathologies. Furthermore, we discuss the shift towards individualized treatment strategies that consider patient-specific factors such as age, reproductive plans, and comorbidities, facilitating tailored therapies. Special attention is given to the role of medical therapies ranging from hormonal treatments to novel non-hormonal drugs, as well as the consideration of minimally invasive surgical options as part of a comprehensive management strategy. By integrating current research findings with clinical practice guidelines, this article aims to provide a synthesized view of the dynamic field of AUB management, proposing a multidisciplinary approach to enhance patient outcomes in premenopausal women.

Keywords: Abnormal uterine bleeding, premenopausal women, personalized medicine, molecular diagnostics

Abnormal uterine bleeding (AUB) in premenopausal women represents a significant diagnostic and therapeutic challenge within the field of gynecology. AUB disrupts the normal menstrual cycle, characterized by deviations in the frequency, volume, and duration of menstrual bleeding. This condition is a predominant health concern not only due to its prevalence but also because of its profound impact on a woman's quality of life, encompassing physical discomfort, emotional distress, and social or occupational disruptions [1].

The management of AUB has historically been dictated by a combination of empirical approaches and a limited understanding of its etiology. However, advancements in medical technology and a deepening of our pathophysiological understanding have ushered in an era of more targeted and effective management strategies [2-4]. These advances facilitate a move away from the "one-size-fits-all" approach, toward more personalized medical care, tailored to the unique needs of each patient based on specific diagnostic data [5].

The International Federation of Gynecology and Obstetrics (FIGO) provides a classification system that categorizes AUB into structural and non-structural

causes, known respectively as PALM (Polyps, Adenomyosis, Leiomyomas, Malignancy) and COEIN (Coagulopathies, Ovulatory dysfunctions, Endometrial, Iatrogenic, Not yet classified). This classification system aids clinicians in pinpointing the precise etiology of AUB, thereby guiding appropriate and specific treatment modalities [2, 6].

The diagnostic process for AUB has become increasingly sophisticated, incorporating a range of modalities such as transvaginal ultrasonography, which offers a first-line non-invasive method that can identify structural causes of AUB with high accuracy. Magnetic resonance imaging (MRI) and hysteroscopy serve as additional diagnostic tools that provide detailed anatomic and functional insights, particularly useful in complex cases where initial imaging may not yield definitive results [7-9].

From a therapeutic perspective, the paradigm shift toward medical management has reduced the reliance on invasive surgical procedures. Medications such as tranexamic acid and non-steroidal anti-inflammatory drugs (NSAIDs) effectively manage bleeding and pain associated with AUB [10]. Hormonal therapies, including the use of oral contraceptives and progesterone therapies, not only regulate menstrual cycles but also treat underlying disorders like endometrial hyperplasia. For cases where medical management is insufficient or inappropriate, minimally invasive surgical options such as endometrial ablation or resectoscopic myomectomy are considered, which preserve uterine integrity and offer rapid recovery [11, 12]. Moreover, the role of novel therapies and emerging technologies cannot be overstated. The development of new pharmaceutical agents targeting specific pathways involved in endometrial proliferation and angiogenesis presents a promising horizon for those affected by AUB. Likewise, advancements in surgical technology continue to refine the safety and efficacy of procedures, minimizing their invasiveness and associated risks [5, 13].

The aim of this review is to critically analyze the latest advancements in the diagnosis and management of AUB, reflecting on how these have transformed clinical practices and improved patient outcomes. This article seeks to synthesize current research findings with established clinical guidelines to offer a comprehensive perspective on the most effective strategies for managing this condition. The review's significance lies in its potential to guide clinicians towards more precise diagnostic techniques and tailored therapeutic interventions, thus ensuring better management of AUB, minimizing invasive procedures, and enhancing the quality of life for affected women.

Despite considerable advancements in medical technology and understanding, many women with AUB still undergo unnecessary invasive procedures due to misdiagnosis or suboptimal management. Addressing this issue, our review highlights the importance of using a systematic approach for diagnosis, based on the FIGO classification system, which categorizes AUB into structural (PALM) and non-structural (COEIN) causes. This classification is crucial for directing specific, cause-based therapeutic strategies which can range from pharmacological treatments to conservative surgical interventions.

Moreover, this article emphasizes the role of new diagnostic tools, including advanced imaging techniques and molecular diagnostics, in enhancing the precision of AUB diagnostics. These technological advancements not only help in identifying the specific types of AUB more accurately but also play a pivotal role in monitoring treatment efficacy and predicting outcomes. The review also delves into the latest therapeutic options, including the increasing use of medical management over surgical interventions. It assesses the efficacy of newer pharmacological agents that target specific pathophysiological pathways involved in AUB, thus offering personalized treatment options that align with the individual patient profiles.

PATHOPHYSIOLOGY OF ABNORMAL UTERINE BLEEDING

Understanding the Biological Foundations
Abnormal uterine bleeding (AUB) in premenopausal women encompasses a spectrum of symptoms that deviate from normal menstrual patterns, characterized by irregularity in timing, volume, or duration of menstrual flow. The complexity of AUB stems from the orchestrated processes governed by the hypothalamic-pituitary-ovarian (HPO) axis, which regulates the menstrual cycle through a precise hormonal balance [14, 15]. Disruptions in this system can lead to a range

of menstrual irregularities collectively referred to as AUB.

The menstrual cycle itself is divided into several phases, each marked by specific hormonal activities. The follicular phase begins with the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates the anterior pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [16]. These hormones promote follicle development and estrogen production from the ovaries. Mid-cycle LH surge triggers ovulation, releasing the egg and initiating the luteal phase, during which the corpus luteum forms and produces progesterone. This hormone is crucial for stabilizing the endometrial lining and preparing it for potential pregnancy. If pregnancy does not occur, progesterone levels fall, leading to the shedding of the endometrial lining as menstruation [17].

Disruptions in any part of this cycle can lead to AUB. These disruptions can be caused by a wide range of factors, including hormonal imbalances, structural abnormalities within the uterus, or systemic medical conditions. To systematically diagnose and manage AUB, the International Federation of Gynecology and Obstetrics (FIGO) has developed a classification system known as PALM-COEIN [18, 19]. This system categorizes the causes of AUB into structural causes (PALM: Polyps, Adenomyosis, Leiomyomas, Malignancy) and non-structural causes (COEIN: Coagulopathies, Ovulatory dysfunctions, Endometrial, Iatrogenic, Not classified). Understanding this classification is crucial for clinicians to direct specific investigations and treatments [20].

FACTORS INFLUENCING ABNORMAL UTERINE BLEEDING

Hormonal Influence

Hormones play a pivotal role in the pathophysiology of AUB. An imbalance in estrogen and progesterone levels is a common culprit. In conditions such as polycystic ovary syndrome (PCOS), ovulatory dysfunction can lead to prolonged estrogen exposure without progesterone counterbalance, causing endometrial hyperplasia and irregular bleeding. Similarly, thyroid dysfunctions can disrupt the hormonal balance necessary for regular menstruation, leading to AUB [18, 21].

Endometrial Environment

At the cellular level, the endometrial environment itself is critical in the development of AUB. Local factors within the uterus, such as the presence of polyps or fibroids, can mechanically disrupt the endometrium, leading to bleeding. Moreover, adenomyosis, where endometrial tissue grows into the uterine muscle, creates a hyper-vascular environment that is prone to bleeding. Angiogenic factors, such as vascular endothelial growth factor (VEGF), are often elevated in these conditions, promoting further vascular instability and bleeding [19].

Systemic Conditions

Systemic medical conditions also significantly influence menstrual bleeding. Coagulation disorders, such as von Willebrand disease, impair the blood's ability to clot, which can manifest as increased menstrual bleeding or AUB. Liver disease affects the metabolism of hormones such as estrogen and progesterone, leading to hormonal imbalances that can cause AUB. Even medications, particularly anticoagulants or hormone therapies, can induce AUB as a side effect [20, 21].

Integrative View on AUB

Addressing AUB effectively requires an integrative approach that considers these multifaceted contributions to the pathology. Clinicians must evaluate hormonal levels, assess for structural anomalies via imaging like ultrasound or MRI, and consider systemic medical conditions that could be contributing to the symptoms. This comprehensive approach ensures that treatment strategies are targeted not just to symptom management but to the underlying causes, enhancing the effectiveness of interventions and patient outcomes [22].

In conclusion, the pathophysiology of AUB is complex and influenced by an array of factors including hormonal imbalances, structural abnormalities, and systemic conditions. Understanding these factors is crucial for the effective management of AUB. Employing the FIGO classification system facilitates a structured diagnostic approach, allowing clinicians to tailor interventions accurately and manage AUB effectively, thereby improving the quality of life for affected women [23]. This comprehensive

understanding also underscores the importance of on-going research and education to continuously refine the approaches to diagnosing and treating this prevalent and impactful health issue.

DIAGNOSTIC APPROACHES TO ABNORMAL UTERINE BLEEDING

Clinical Evaluation

The initial approach to diagnosing abnormal uterine bleeding (AUB) involves a thorough clinical evaluation that establishes a comprehensive understanding of the patient's symptoms and medical history. This step is crucial as it guides the subsequent diagnostic pathway and informs potential therapeutic strategies [24-27].

The clinical evaluation begins with a detailed medical history that should cover the duration, frequency, and volume of menstrual bleeding. Clinicians should ask about the regularity of menstrual cycles, the presence of any associated symptoms such as pelvic pain, and the impact of bleeding on daily activities. Medical history should also include inquiries into reproductive history, including pregnancies, childbirth, and any gynecological surgeries or conditions such as fibroids or endometriosis [24].

Physical examination is another foundational element of the clinical evaluation and typically includes a pelvic exam. During the pelvic exam, clinicians assess the size and shape of the uterus and ovaries, check for any abnormalities or masses, and evaluate signs of hormonal imbalances such as hirsutism or acne. The examination might also involve a Pap test to check for cervical dysplasia or cancer if the patient is due for screening [23].

Documenting symptoms accurately is vital for diagnosing AUB. The use of symptom diaries, where patients record the days they bleed and note the heaviness of the flow, can provide valuable insights into the pattern of bleeding. This documentation aids in differentiating between various types of AUB and is essential for aligning with the FIGO classification for more targeted investigations [24, 26].

Advanced Diagnostic Tools

After the initial clinical evaluation, more specific diagnostic tools can be employed to further investigate the causes of AUB. The selection of these tools often depends on the findings from the clinical evaluation and the suspected underlying causes [26].

Transvaginal Ultrasound

Transvaginal ultrasound (TVUS) is often the first-line imaging tool due to its non-invasive nature and effectiveness in evaluating pelvic structures. TVUS can provide detailed images of the uterus, endometrium, and ovaries, allowing for the identification of structural causes of AUB such as polyps, fibroids, and adenomyosis. It can also assess the thickness and texture of the endometrium, which is crucial for diagnosing endometrial hyperplasia or other intrauterine abnormalities. The major strengths of TVUS include its accessibility, cost-effectiveness, and detailed visualization of pelvic anatomy. However, its limitations lie in its operator dependency and less effectiveness in patients with a high body mass index or those with extensive pelvic scarring [23, 25].

Magnetic Resonance Imaging (MRI)

MRI is used selectively for diagnosing AUB, particularly when TVUS results are inconclusive or when more detailed imaging of the uterine myometrium is necessary. MRI is highly sensitive and specific for diagnosing adenomyosis and distinguishing it from other uterine pathologies like fibroids. Its multiplanar imaging capability provides a comprehensive view of the pelvic anatomy without radiation exposure. However, MRI is more expensive, less available, and requires more time for both performing the scan and interpreting the results compared to TVUS [26].

Hysteroscopy

Hysteroscopy is an invasive procedure that allows direct visualization of the uterine cavity and is used when there is a need to assess intrauterine pathologies that might not be adequately visualized by imaging studies alone. It is particularly useful for diagnosing and sometimes treating uterine polyps, submucosal fibroids, and focal areas of endometrial hyperplasia. Hysteroscopy provides the advantage of direct visualization and the ability to perform therapeutic interventions simultaneously, such as polypectomy or biopsy. Its limitations include the need for anesthesia, the risks associated with invasive procedures, and its dependency on the skill and experience of the operator [27].

The Role of Laboratory Tests

Laboratory tests play a complementary role in the diagnosis of AUB. Blood tests, hormonal panels, and biopsy procedures are critical, especially when non-structural causes of AUB are suspected [28-30].

Blood Tests

Complete blood count (CBC) can detect anemia, which may result from chronic heavy menstrual bleeding. Coagulation profiles (PT, aPTT) are essential if a bleeding disorder is suspected. Thyroid function tests are also recommended as hypothyroidism or hyperthyroidism can cause menstrual irregularities [30].

Hormonal Panels

Hormonal assessments include measuring levels of estrogen, progesterone, LH, FSH, and prolactin, particularly when endocrine disorders or ovulatory dysfunctions are suspected. These tests help in understanding the hormonal milieu that may be contributing to AUB [31].

Endometrial Biopsy

An endometrial biopsy is indicated if there is a suspicion of endometrial hyperplasia or cancer, especially in women over the age of 35 or those with risk factors such as obesity or PCOS. This procedure involves sampling the endometrial tissue and is typically performed if the endometrial thickness on ultrasound is greater than the normal limits for the patient's age and reproductive status [24, 30].

In summary, the diagnostic approach to AUB involves a multi-faceted strategy incorporating clinical evaluation, advanced imaging, and laboratory testing. Each diagnostic tool or procedure provides unique and complementary insights, which collectively contribute to a comprehensive understanding of the etiology of AUB. This rigorous diagnostic process is essential for developing an effective and individualized management plan for women suffering from AUB, ultimately aiming to improve their quality of life and reproductive health outcomes.

MANAGEMENT OF ABNORMAL UTERINE BLEEDING

First-line Medical Therapies

The medical management of abnormal uterine bleeding (AUB) aims to alleviate symptoms, improve quality of life, and address underlying pathologies. First-line therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), tranexamic acid, oral contraceptives (OCs), and hormonal intrauterine devices (IUDs), each offering unique mechanisms of action and benefits.

NSAIDs

NSAIDs inhibit prostaglandin synthesis, thereby reducing menstrual blood flow and alleviating associated pain. These drugs are particularly effective in women with dysmenorrhea or heavy menstrual bleeding. By inhibiting prostaglandin production, NSAIDs not only reduce menstrual flow but also mitigate associated symptoms such as pelvic discomfort and cramping. Commonly used NSAIDs include ibuprofen, naproxen, and mefenamic acid. While generally well-tolerated, NSAIDs may cause gastrointestinal irritation or renal impairment, necessitating caution in patients with preexisting gastrointestinal disorders or renal insufficiency [28].

Tranexamic Acid

Tranexamic acid is an antifibrinolytic agent that promotes blood clotting by inhibiting the breakdown of fibrin, thereby reducing menstrual blood loss. It is highly effective in reducing the volume and duration of menstrual bleeding, particularly in women with menorrhagia or bleeding disorders. Tranexamic acid is typically administered orally and can be initiated at the onset of menstruation or upon the onset of heavy bleeding. While generally safe, caution is advised in patients with a history of thromboembolic events or those at risk of thrombosis [29].

Oral Contraceptives (OCs)

Oral contraceptives are commonly prescribed as first-line therapy for AUB due to their ability to regulate menstrual cycles and reduce menstrual bleeding. Combined oral contraceptives containing both estrogen and progestin suppress ovulation, stabilize the endometrium, and reduce menstrual flow. They also offer additional benefits such as contraception and relief from menstrual-related symptoms such as dysmenorrhea and premenstrual syndrome. Progestin-only pills or continuous-cycle regimens may be preferred in women with contraindications to es-

trogen or those seeking non-contraceptive benefits of OCs. Potential side effects of OCs include nausea, breast tenderness, and breakthrough bleeding, although these typically resolve with continued use [30].

Hormonal Intrauterine Devices (IUDs)

Hormonal IUDs, such as levonorgestrel-releasing intrauterine systems (LNG-IUDs), offer an effective and long-term solution for managing AUB. These devices release progestin locally into the uterine cavity, resulting in endometrial suppression, reduced menstrual flow, and amenorrhea in some cases. LNG-IUDs are particularly suitable for women with heavy menstrual bleeding, as they offer a non-systemic hormonal approach with minimal side effects. Additionally, LNG-IUDs provide long-acting contraception, making them a convenient option for women seeking dual benefits of contraception and menstrual regulation. Insertion of an LNG-IUD is a minor procedure typically performed in an office setting, with potential side effects including irregular bleeding, cramping, and expulsion [31].

New Pharmacological Treatments

In addition to traditional first-line therapies, emerging pharmacological treatments offer promising avenues for the management of AUB by targeting specific pathophysiological pathways.

Gonadotropin-Releasing Hormone (GnRH) Agonists

GnRH agonists suppress the pituitary-ovarian axis, resulting in hypoestrogenism and amenorrhea. These agents are particularly useful in the management of AUB associated with estrogen-dependent conditions such as uterine fibroids or endometriosis. While highly effective in reducing menstrual bleeding and alleviating symptoms, GnRH agonists are associated with menopausal-like side effects such as hot flashes, vaginal dryness, and bone loss. Consequently, they are typically used as short-term therapy or as preoperative adjuncts to reduce uterine size and vascularity before definitive surgical management [32].

Selective Progesterone Receptor Modulators (SPRMs)

SPRMs are a novel class of drugs that selectively target progesterone receptors in the endometrium, exerting both agonistic and antagonistic effects. By modulating progesterone signaling, SPRMs offer

therapeutic benefits in conditions such as uterine fibroids and endometriosis, where aberrant progesterone action contributes to AUB. Drugs such as ulipristal acetate have demonstrated efficacy in reducing fibroid size, alleviating symptoms, and improving menstrual bleeding patterns. While generally well-tolerated, SPRMs may cause side effects such as headaches, hot flashes, and gastrointestinal disturbances [33].

The medical management of abnormal uterine bleeding encompasses a range of therapeutic options tailored to individual patient needs and preferences. First-line therapies such as NSAIDs, tranexamic acid, oral contraceptives, and hormonal IUDs offer effective symptom relief and menstrual regulation for many women with AUB. Emerging pharmacological treatments, including GnRH agonists and selective progesterone receptor modulators, present promising alternatives for women with refractory AUB or those seeking non-hormonal options. By offering a diverse array of therapeutic modalities, clinicians can effectively address the complex needs of women with AUB, improving their quality of life and reproductive health outcomes [31, 32].

Surgical and Minimally Invasive Interventions
Indications for Surgery

While medical management is often effective for many cases of abnormal uterine bleeding (AUB), there are situations where surgical intervention becomes necessary. Indications for surgery vary depending on the underlying cause of AUB, the severity of symptoms, and the patient's reproductive goals [4, 7].

One common indication for surgery is the presence of structural abnormalities such as large fibroids, polyps, or adenomyosis that do not respond to medical therapies. These conditions can cause significant symptoms such as heavy menstrual bleeding, pelvic pain, and reproductive issues, warranting surgical intervention to alleviate symptoms and improve quality of life. Additionally, women with AUB associated with endometrial hyperplasia or malignancy may require surgical procedures for diagnostic and therapeutic purposes [21].

Several surgical interventions are available for managing AUB, each with its own effectiveness and associated risks. Hysterectomy, the surgical removal of the uterus, is considered the definitive treatment for many cases of AUB, particularly in women who have completed childbearing or who have failed other treat-

ments. While hysterectomy offers a permanent solution to AUB, it is a major surgical procedure associated with risks such as infection, bleeding, and complications related to anesthesia [34].

For women who wish to preserve their fertility or avoid the risks of hysterectomy, less invasive surgical options may be considered. Endometrial ablation is a minimally invasive procedure that destroys the endometrial lining of the uterus, reducing or eliminating menstrual bleeding. This procedure is suitable for women with AUB due to benign causes such as fibroids or adenomyosis who desire symptom relief without compromising fertility. However, endometrial ablation is not suitable for women with endometrial hyperplasia or malignancy [35, 36].

Minimally Invasive Techniques

In addition to endometrial ablation, other minimally invasive techniques are available for managing AUB, each with its own advantages and considerations. Myomectomy, the surgical removal of uterine fibroids, is an option for women with AUB caused by fibroids who wish to preserve their fertility. This procedure can be performed via laparotomy, laparoscopy, or hysteroscopy, depending on the size and location of the fibroids. While myomectomy can improve symptoms and preserve fertility, it is associated with risks such as bleeding, infection, and fibroid recurrence [1, 37].

Uterine artery embolization (UAE) is another minimally invasive option for managing AUB due to fibroids. During UAE, tiny particles are injected into the blood vessels supplying the fibroids, causing them to shrink and reduce menstrual bleeding. UAE is suitable for women who wish to avoid surgery or preserve their fertility, as it does not involve the removal of uterine tissue. However, UAE is associated with risks such as pelvic pain, post-embolization syndrome, and the potential for complications related to fibroid expulsion [15].

Patient selection is crucial when considering minimally invasive interventions for AUB. Factors such as age, reproductive goals, the size and location of uterine abnormalities, and overall health should be carefully assessed to determine the most appropriate treatment option for each individual patient. Additionally, thorough preoperative counseling should be provided to ensure that patients understand the benefits, risks, and expected outcomes of the chosen interven-

tion [2-8].

Surgical and minimally invasive interventions play a crucial role in the management of abnormal uterine bleeding, particularly in cases where medical therapies are ineffective or contraindicated. Indications for surgery vary depending on the underlying cause of AUB and the patient's individual circumstances. While hysterectomy remains a definitive treatment option for many cases of AUB, less invasive techniques such as endometrial ablation, myomectomy, and uterine artery embolization offer alternatives for women who wish to preserve their fertility or avoid major surgery. By carefully evaluating patient needs and selecting the most appropriate intervention, clinicians can effectively manage AUB and improve the quality of life for affected women [31-35].

EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

Innovative Diagnostics and Therapies

Advancements in technology are revolutionizing the diagnosis and treatment of abnormal uterine bleeding (AUB), offering new insights and approaches to improve patient outcomes. Cutting-edge research is exploring innovative diagnostics and therapies that harness the power of artificial intelligence (AI), gene therapy, and other novel technologies [32].

Artificial Intelligence in Diagnostics

One promising area of research is the use of AI in ultrasound analysis for the diagnosis of AUB. AI algorithms trained on large datasets of ultrasound images can automate the detection of structural abnormalities such as fibroids, polyps, and adenomyosis with high accuracy and efficiency [33, 34]. These AI-driven tools have the potential to streamline the diagnostic process, reduce interobserver variability, and improve diagnostic accuracy, particularly in cases where subtle abnormalities may be overlooked by human observers. By enhancing the speed and accuracy of ultrasound analysis, AI technologies hold promise for earlier detection and intervention in women with AUB, leading to improved patient outcomes and reduced healthcare costs [38].

Gene Therapy Approaches

Another area of exploration in AUB research is the

development of gene therapy approaches to target the underlying molecular mechanisms driving abnormal uterine bleeding. Gene therapy holds the potential to correct genetic abnormalities, modulate hormone signaling pathways, and promote tissue regeneration within the uterine cavity [39, 40]. For example, researchers are investigating gene editing techniques such as CRISPR-Cas9 to selectively modify genes associated with endometrial dysfunction or abnormal bleeding patterns. By targeting specific molecular pathways implicated in AUB, gene therapy approaches aim to provide personalized and targeted treatments with minimal side effects, paving the way for more effective and tailored interventions in the future [41].

Integrating Patient-centered Care in AUB Management

Personalized medicine is increasingly shaping the future of AUB treatment, with a focus on integrating patient preferences, values, and lifestyle adjustments into management plans. Patient-centered care emphasizes the importance of involving patients as active participants in their healthcare decisions, tailoring treatments to their individual needs and preferences, and considering the impact of AUB on their quality of life [20].

Tailored Treatment Plans

In the era of personalized medicine, treatment plans for AUB are becoming increasingly tailored to the unique characteristics and preferences of each patient. Clinicians consider factors such as age, reproductive goals, comorbidities, and patient preferences when selecting treatment options, ensuring that interventions align with the patient's values and priorities. Shared decision-making between patients and healthcare providers is central to this approach, empowering patients to actively participate in their care and make informed choices about their treatment options [1, 7, 11].

Lifestyle Modifications

In addition to medical and surgical interventions, lifestyle modifications play an important role in the management of AUB. Patients may be advised to make dietary changes, incorporate regular exercise into their routine, manage stress levels, and optimize their overall health to support hormonal balance and menstrual regularity. Integrating lifestyle modifica-

tions into AUB management plans can complement medical therapies, improve treatment outcomes, and enhance the overall well-being of patients [42].

The future of AUB diagnosis and treatment is shaped by innovative technologies, personalized medicine, and a patient-centered approach to care. Advancements in AI-driven diagnostics and gene therapy hold promise for earlier detection, targeted interventions, and improved outcomes for women with AUB. By integrating patient preferences, values, and lifestyle adjustments into management plans, clinicians can provide more personalized and effective care that addresses the unique needs of each individual patient. As research continues to advance and technology evolves, the landscape of AUB management will continue to evolve, offering new opportunities to optimize patient care and improve quality of life.

CHALLENGES AND CONSIDERATIONS IN ABNORMAL UTERINE BLEEDING MANAGEMENT

Managing AUB in Diverse Populations

Treating AUB poses unique challenges across different demographic groups, requiring clinicians to consider a range of factors such as age, reproductive intentions, and co-existing medical conditions [37, 41].

Age-related Considerations

Age plays a significant role in AUB management, as the etiology and optimal treatment approach may vary depending on the patient's reproductive stage. Adolescents experiencing AUB may have underlying hormonal imbalances or anatomical abnormalities, necessitating thorough evaluation and tailored interventions. In contrast, perimenopausal and postmenopausal women may present with AUB due to endometrial pathology or hormonal fluctuations, requiring different diagnostic and therapeutic strategies. Additionally, older women may have comorbidities that impact treatment decisions, highlighting the importance of a multidisciplinary approach to care [42].

Reproductive Intentions

The reproductive intentions of women with AUB influence treatment decisions, particularly regarding fertility preservation and contraceptive needs. For women desiring future pregnancies, interventions such

as myomectomy or fertility-sparing endometrial ablation may be considered to address underlying causes of AUB while preserving reproductive potential [43, 44]. Conversely, women who have completed childbearing may opt for definitive treatments such as hysterectomy to alleviate symptoms and minimize the risk of recurrence. Clinicians must engage in shared decision-making with patients to align treatment plans with their reproductive goals and preferences [45].

Co-existing Medical Conditions

Managing AUB in patients with co-existing medical conditions presents additional complexities, as underlying health issues may impact treatment options and outcomes. Women with conditions such as obesity, diabetes, thyroid disorders, or bleeding disorders may require tailored approaches to AUB management to optimize safety and efficacy. Furthermore, medications used to manage chronic conditions may interact with AUB therapies, necessitating careful consideration and coordination of care to minimize adverse effects and drug interactions [42].

Quality of Life and Psychosocial Aspects

The impact of AUB extends beyond physical symptoms, significantly affecting quality of life and psychosocial well-being. Heavy menstrual bleeding, pain, and unpredictable bleeding patterns can impair daily activities, work productivity, social interactions, and intimate relationships, leading to emotional distress and reduced quality of life. Women with AUB may experience anxiety, depression, social isolation, and impaired self-esteem, highlighting the importance of holistic care that addresses psychosocial needs alongside medical management [7, 39].

Supportive Care and Counseling

Supportive care and counseling are integral components of AUB management, providing emotional support, education, and coping strategies to help women navigate the challenges of living with AUB. Clinicians should create a supportive and non-judgmental environment where patients feel comfortable discussing their symptoms, concerns, and treatment preferences. Patient education about the etiology of AUB, available treatment options, and expected outcomes empowers women to make informed decisions and actively participate in their care. Additionally,

counseling on lifestyle modifications, stress management techniques, and self-care practices can enhance resilience and improve overall well-being [41, 42].

Managing AUB requires a comprehensive and individualized approach that considers the diverse needs and circumstances of affected women. Clinicians must navigate challenges related to age, reproductive intentions, and co-existing medical conditions while prioritizing patient-centered care and psychosocial support. By addressing these challenges and considerations in AUB management, clinicians can optimize treatment outcomes, improve quality of life, and enhance the overall well-being of women affected by this common and impactful condition.

CONCLUSIONS

The field of gynecology has witnessed substantial progress in the management of abnormal uterine bleeding (AUB) among premenopausal women. This progression has moved from a conventional, broad-spectrum approach towards a highly sophisticated, individualized methodology. Developments in diagnostic technologies, notably transvaginal ultrasonography, magnetic resonance imaging (MRI), and hysteroscopy, combined with advances in molecular diagnostics, have revolutionized our diagnostic capabilities. Such enhancements in diagnostic accuracy are critical as they provide a foundation for developing personalized therapeutic interventions that are intricately aligned with the unique pathophysiological conditions of each patient.

The systematic application of the International Federation of Gynecology and Obstetrics (FIGO) classification system has been pivotal. It serves as a structured framework that assists clinicians in pinpointing the specific etiologies of AUB, thereby facilitating the implementation of targeted medical and surgical interventions. This nuanced understanding allows for a shift towards primarily medical management, utilizing hormonal therapies and cutting-edge pharmacological agents. This approach reflects a paradigm shift focused on reducing the dependence on invasive surgical procedures and enhancing overall patient outcomes.

Ongoing advancements in technology and the integration of personalized medicine principles are continually refining management strategies for AUB. These include an emphasis on minimally invasive sur-

gical techniques when necessary and a focus on patient-centered care. The field stands on the cusp of further transformative developments with the anticipated integration of artificial intelligence in diagnostic processes and gene therapy in treatment protocols. These innovations promise to further elevate the precision of diagnostics and the effectiveness of treatments.

However, the management of AUB still presents significant challenges, particularly when addressing the needs of diverse populations that may have different reproductive intentions and coexist with various medical conditions. An effective management strategy requires a comprehensive multidisciplinary approach that encompasses not only advanced diagnostic and therapeutic techniques but also a strong emphasis on patient education and psychosocial support. This approach ensures that all aspects of a patient's health and well-being are considered, making the management of AUB more holistic and patient-focused.

Moreover, the quality of life implications for women suffering from AUB cannot be overstated. The physical, emotional, and social burdens of this condition necessitate that therapeutic approaches not only address the physiological aspects of the disease but also the psychological and social impacts. Supportive care, encompassing counseling and lifestyle advice, plays a critical role in this context, providing patients with the tools needed to manage their condition effectively.

As we continue to advance in our understanding and capabilities, the integration of these new technologies and methodologies into everyday clinical practice remains essential. Doing so not only optimizes therapeutic outcomes but also significantly enhances the quality of life for women affected by AUB. This ongoing evolution in the field underscores the critical need for continuous research, innovation, and education in gynecology to keep pace with emerging technologies and changing patient needs. The future of AUB management looks promising, with the potential to offer more precise, effective, and less invasive options for women worldwide.

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Eisenmenger syndrome presenting with chronic thromboembolic disease

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ABSTRACT

Objectives: Eisenmenger syndrome is characterized by the reversal of blood flow due to increased pulmonary vascular resistance. It can be prevented with early diagnosis and surgical treatment. Thromboembolism is a leading cause of death in patients with Eisenmenger syndrome. Pulmonary endarterectomy is the primary treatment, but medical treatments may be considered in inoperable cases. Regular follow-up and a multidisciplinary approach are important for diagnosis and treatment. Lifestyle changes and medical therapy can improve patient's quality of life and prevent complications. Our case is presented because of the chronic thromboembolic disease in addition to the pulmonary hypertension due to the partial atrioventricular septal defect and the management of the treatment.

Keywords: Eisenmenger syndrome, pulmonary hypertension, chronic thromboembolic disease

*E*isenmenger syndrome (ES) is defined as the reversal of blood flow (pulmonary-systemic shunt) or bidirectionality of blood flow due to a severe increase in pulmonary vascular resistance (PVR) in the largest systemic-pulmonary shunts. ES often occurs in people with heart disease. The most frequent cardiac diseases include congenital heart diseases (CHD) such as ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA) [1]. Erythrocytosis, hyperviscosity, and multiple organ system involvement develop as a result of chronic hypoxia. Treatment of ES may vary according to the severity of symptoms and the patient's age. The aim is to improve heart and lung function and reduce symptoms. Treatment options include drug therapy, oxygen therapy, surgical interventions, and other procedures [2]. Our case is presented because of the chronic thromboembolic disease (CTEH) in addition to the pulmonary hypertension due to the partial atrioventricular septal defect (AVSD) and the management of the treatment.

CASE PRESENTATION

A 66-year-old woman presented to our emergency department with pre-syncope. The patient's oxygen saturation was 60%, respiratory rate was 18/min and arterial blood pressure was 180/110. In history, it was learned that the patient had limited exertion and cyanosis for a long time. Antero-posterior chest radiography showed enlargement of the right hilum and increased density in the left middle and lower zones (Fig. 1). On pulmonary computed tomographic an-
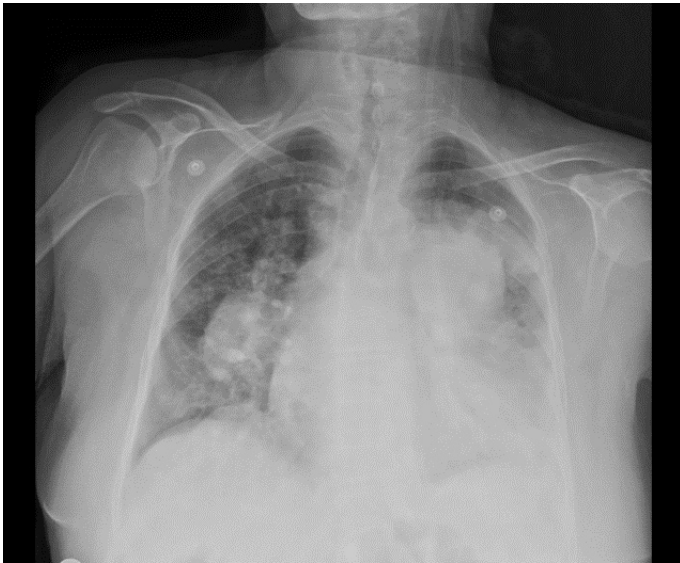

Fig. 1. Antero-posterior chest radiography showed enlargement of the right hilum and increased density in the left middle and lower zones.

giography (CTA), the diameter of the pulmonary artery was approximately 74 mm at its widest point, the diameter of the right main pulmonary artery was 52 mm, the diameter of the left main pulmonary artery was 41 mm at its widest point, and chronic thrombus formation was present in the right main pulmonary artery, middle lobe and lower lobe branches (Figs. 2a and 2b). Echocardiographic examination revealed a single AV valve, partial atrioventricular septal defect (AVSD), pulmonary artery diameter 8 cm, dilated atria, left-sided ventricle hypertrophic, mean pulmonary artery pressure (mPAP): 55 mmHg (Fig. 3).

Right heart catheterization was performed (mPAP: 77 mmHg, pulmonary capillary wedge pressure (PCWP): 13 mmHg, PVR: 7.68 WU, vasoreactivity test was negative). The patient's functional classification (FS) was IV according to the New York Heart Association and anticoagulant, diuretic, endothelin receptor antagonist (ERA), and long-term oxygen therapy (LTOT) treatment was started. At the 3-month treatment control, the patient regressed to FS-III, mean PAP: 45 mmHg, and thrombus burden on CTA continued to decrease with a decrease in thrombus burden and was considered inoperable for endarterectomy, so Riociguat was added to the treatment. At the 6th-month treatment check, the patient's resting oxygen saturation was 92% and FS was III, so it was decided to continue clinical follow-up.

DISCUSSION

Eisenmenger syndrome and CTEH are two different entities causing pulmonary arterial hypertension (PAH) with different pathophysiological mechanisms. In cases of Eisenmenger's syndrome due to congenital heart disease, pulmonary hypertension can be prevented with early diagnosis and surgical treatment, and PAH-specific treatments can provide hemodynamic improvement in delayed cases reaching adulthood [1]. The risk of thromboembolism has been studied in several cohorts of congenital heart disease. The results have been variable, depending on the study, the size of the population, and the study methods. Importantly, the risk varies according to the type and complexity
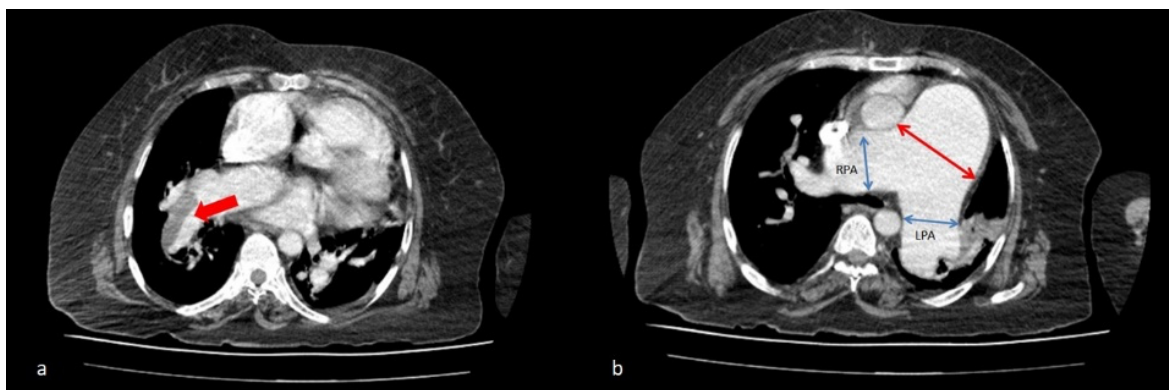

Fig. 2. (a) Chronic thrombus formation in the right main pulmonary artery (red arrow), (b) Enlarged Pulmonary truncus (red line), enlarged right and left main pulmonary artery (blue line).
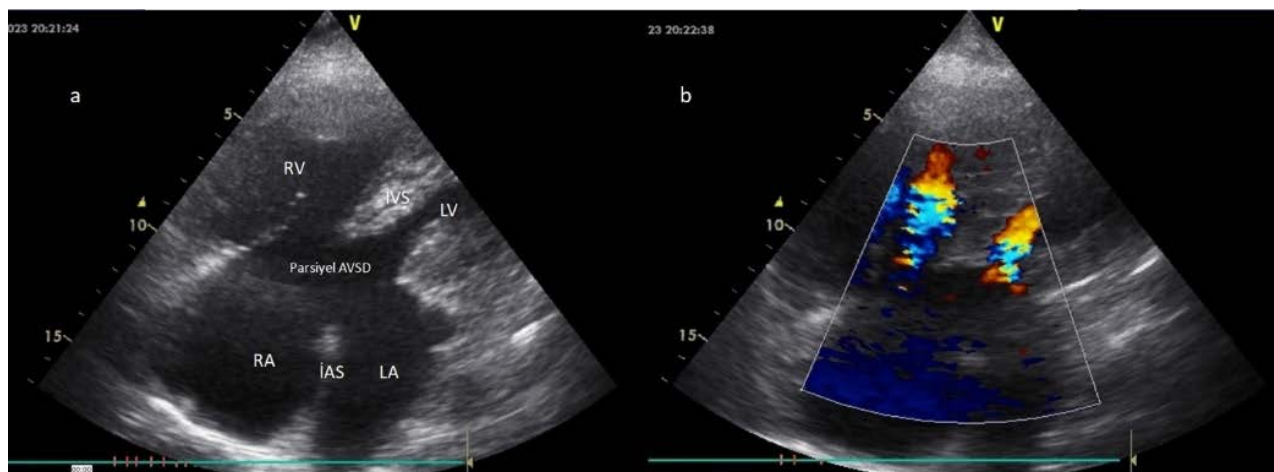
Fig. 3. Partial atrio-ventricular septal defect (AVSD) appearance on echocardiogram.

of the CHD; patients with transposition of the great arteries, univentricular hearts, and cyanotic CHD are at increased risk [4, 5]. There is a significant risk of pulmonary artery thrombus formation in 21-29% of patients with Eisenmenger syndrome [6]. In the study of 34 patients with ES by Silversides K *et al.* the prevalence of proximal pulmonary artery thrombi was 21% (7/34). Thrombosis of more distal vessels was detected in 43% (3/7%) of patients with thrombus in the proximal pulmonary arteries, and patients with thrombus were more likely to be female (86% vs. 37%, P=0.04) and to have lower oxygen saturation (72±9% vs. 85±6%, P=0.01) [7]. Hjortshøj *et al.* [8] in a retrospective study of 1546 patients between 1977 and 2015 to determine cause-specific mortality in ES, thromboembolism was found to be 8% of the leading causes of death. CTEH is also a condition that should be evaluated among the etiological causes of PAH. Although the primary treatment is pulmonary endarterectomy in appropriate cases, medical treatments should be considered in inoperable cases [3].

CONCLUSION

Pulmonary hypertension is a serious health problem and early diagnosis and treatment are very important. The association of Eisenmenger's syndrome and CTEH is a rare condition that can have serious consequences. The diagnosis and treatment of these conditions requires a multidisciplinary approach and regular follow-up of patients is important. Medical therapy, surgical intervention, and lifestyle changes play an important role in the management of these diseases. This can improve patients' quality of life and prevent serious complications.

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