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Effects of the COVID-19 pandemic on the emergency management of patients presenting with ST-elevation myocardial infarction

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ABSTRACT

Objectives: This study aims to analyze the changes in the emergency management of ST-elevation myocardial infarction (STEMI) patients during the coronavirus disease 2019 (COVID-19) pandemic.

Patients and methods: A total of 474 individuals (375 males, 99 females; mean age: 61.7±12.7 years; range, 22 to 93 years) who presented to the emergency department with STEMI between March 1, 2019, and March 1, 2021, were included in the study. The impact of the pandemic on the management of STEMI patients was assessed by comparing the patients in two time periods: the pre-COVID-19 period (n=271) and the COVID-19 pandemic (n=203). Archive records were retrospectively examined to assess the pandemic's impact on various aspects, including arrival time at the emergency department, consultation duration, time from arrival to percutaneous coronary intervention, treatment choice, in-hospital mortality rate, and length of inpatient stay.

Results: There was a notable decrease in the proportion of patients arriving within 2 h of symptom onset during the COVID-19 era ($p<0.05$). The mean time for STEMI patients to be referred to the cardiology clinic was 15.90±21.97 min. Additionally, the door-to-needle time was faster during the COVID-19 era compared to the prepandemic period.

Conclusion: Despite the prolonged duration of presentation to the emergency department for patients exhibiting symptoms of STEMI during the COVID-19 era, there was no extension in the consultation and door-to-needle times for patients diagnosed with STEMI.

Keywords: Acute coronary syndromes, myocardial revascularization, pandemic percutaneous coronary intervention.

Cardiovascular diseases are a prevalent cause of mortality worldwide. In the year 2022, approximately 35.4% of deaths were attributed to disorders of the circulatory system. This global burden affects a significant population of 18 million individuals. The primary cause of mortality in relation to cardiovascular diseases is coronary artery disease, specifically characterized by the accumulation of atherosclerotic plaques in the coronary arteries over time.[1] While this condition may remain stable for an extended duration, it can transition into an unstable state as a consequence of atherothrombotic events following plaque rupture.[2] Numerous risk factors contribute to the development of coronary artery disease, including smoking, diabetes, hyperlipidemia, hypertension, male gender, a family history of the condition, and obesity.[3] Managing these risk factors is imperative in the prevention of coronary artery disease and in enhancing the efficacy of applied therapeutic interventions.[4]

Acute myocardial infarction occurs due to acute myocardial ischemia, resulting in the necrosis of cardiomyocytes.[5] A clinical manifestation of acute myocardial infarction is ST-elevation myocardial infarction (STEMI), characterized by the presence of ST-segment elevation on the electrocardiogram and symptoms indicative of myocardial ischemia. It arises from the complete occlusion of the coronary artery and necessitates immediate medical attention.[6] Failure to promptly restore blood flow to the affected area leads to transmural

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necrosis. The extent of necrosis is influenced by the duration of revascularization, with prolonged intervals resulting in the expansion of the necrotic region and reduced salvage of myocardial tissue.[7] The prognosis of STEMI is closely associated with the salvaged myocardial area. Two interventions are employed to achieve revascularization in patients with STEMI: primary percutaneous coronary intervention (PCI) and thrombolytic therapy. Primary PCI is the recommended first-line treatment for individuals experiencing STEMI.[8]

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on healthcare services, with enduring consequences. Originating in Wuhan, China, in December 2019, the World Health Organization (WHO) declared it a pandemic on March 11, 2020. As of October 4, 2023, the WHO has reported a total of 771,151,224 confirmed cases of COVID-19, resulting in 6,960,783 deaths. The pandemic necessitated the allocation of a significant portion of healthcare resources to the management of COVID-19 patients. Consequently, the emergency management of various diseases, including STEMI, underwent modifications. Many countries implemented quarantine measures and social distancing protocols, leading to the postponement of elective procedures in hospitals. In conjunction with the public's fear of contracting COVID-19, this resulted in a substantial decrease in non-COVID-19-related patient admissions, including those with STEMI. Consequently, the time interval between the onset of symptoms and treatment for STEMI patients increased, accompanied by a reduction in the number of primary PCIs performed. The extended delay in treatment initiation has subsequently contributed to elevated mortality rates.[9] During the COVID-19 era, it was found that STEMI patients who tested positive for COVID-19 had a higher mortality rate and were more likely to be hospitalized for heart failure during long-term follow-up.[10] This study aimed to analyze the changes in the emergency management of STEMI patients during the pandemic.

PATIENTS AND METHODS

The single-center retrospective observational study was conducted with 474 patients. Records of patients who sought medical attention at the emergency department of the Dokuz Eylül University Hospital between March 1, 2019, and March 1, 2021, were examined. The inclusion criteria for the study were patients who were diagnosed with STEMI. Conversely, individuals who exhibited another medical condition leading to ST-segment elevation, encountered difficulties in accessing angiography notes, or had incomplete archive records were excluded from the study. Consequently, a total of 474 patients (375 males, 99 females; mean age: 61.7±12.7 years; range, 22 to 93 years) were included in this study, while a subset of 23 patients who fulfilled at least one of the exclusion criteria were not incorporated in the analysis. The patients were assessed in two distinct time periods to assess the changes in the emergency management of STEMI patients during and before the pandemic: the pre-COVID-19 period (2019-2020), which included 271 patients, and the COVID-19 pandemic (2020-2021), which included 203 patients.

The data pertaining to patients who fulfilled the specified criteria was duly documented in accordance with the prescribed data form of the study. The data was gathered from the hospital's information management system and the record archives of the Department of Cardiology and the Department of Emergency Medicine. The study involved scanning archive records for sex, age, demographic characteristics, vital signs, admission times, symptom durations, arrival options to the hospital, accompanying diseases, risk factors, electrocardiogram findings, diagnosis and consultation durations, treatment decisions, treatment outcomes, in-hospital mortality, and length of hospitalization.

The treatment decisions were classified as follows: patients who underwent coronary angiography (CAG) within the initial 2-h period were designated as very urgent CAG. Individuals who underwent CAG between 2 to 8 h were classified as urgent CAG. Those who solely received thrombolytic treatment without undergoing CAG were categorized separately. The duration between the patient's arrival at the emergency department and their subsequent undergoing of CAG was defined as door-to-needle time. To evaluate the impact of the pandemic on the duration between symptom onset and emergency department presentation, we analyzed arrival times and classified them into four subcategories: <2 h, 2 to 6 h, 6 to 12 h, and >12 h. Furthermore, the patients' arrival times were categorized based on whether they occurred during regular working hours (08:00-17:00) or outside of these hours (17:00-08:00).

Statistical analysis

The data underwent statistical analysis utilizing the IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistical analyses were executed for all data, with the determination of their frequencies. Comparative statistical analyses, in accordance with the hypothesis, were conducted utilizing the independent sample t-test and Pearson's chi-square test, contingent upon the type of variable. The variables were derived from patient information extracted from the data form. A p-value <0.05 was considered statistically significant.

RESULTS

A statistically significant association was observed between sex and the occurrence of STEMI (p=0.002). Moreover, the study assessed the impact of working hours on patient arrival times, distinguishing between daytime (08:00-17:00) and nighttime (17:00-08:00). Out of the total patient population, 167 (35.2%) individuals arrived during the day, whereas 307 (64.8%) patients presented during the night. However, the analysis did not reveal a statistically significant difference in admission times (p=0.053). The investigation also compared the duration of symptoms between the pre-COVID-19 and COVID-19 periods, stratifying the intervals into 0-2 h, 2-6 h, 6-12 h, and >12 hours. In the pre-COVID-19 era, the majority of 139 (51.3%) patients sought medical assistance within the 0-2 h time frame. Conversely, during the COVID-19 period, only 68 (33.5%) individuals presented within the same time frame. Notably, a statistically significant difference was observed between these two groups (p=0.002) (Table 1).

After receiving the diagnosis, the mean duration for cardiology consultation in the entire patient population amounted to 15.90±21.97 min. Within the pre-COVID-19 and COVID-19 eras, the minimal duration was 3 min, whereas the maximal duration reached 26 min. There existed no statistically

Table 1
Comparison of all patients according to the pre-COVID-19 and COVID-19 periods (n=474)

	Pre-COVID-19 period (n=271)				COVID-19 period (n=203)				
Variables	n	%	Mean±SD	Min-Max	n	%	Mean±SD	Min-Max	p
Age (year)			61.0+12.6	22-93			62.6+12.9	31-93	
Sex									0.219
Male	211	77.8			164	80.7			
Female	60	22.1			39	19.2			
Appointment time									0.523
08:00-17:00	92	33.9			75	36.9			
17:00-08:00	179	66.1			128	63.1			
Comorbidity and risk factors									
Hypertension	153	56.5			115	56.6			0.798
Diabetes mellitus	89	32.8			74	36.5			0.414
Coronary artery disease	75	27.7			59	29.1			0.740
Hyperlipidemia	17	6.3			2	1			**0.005***
Smoking	113	41.7			140	69.3			**0.005***
COVID-19 history	0	0			0	0			0
Family history	12	4.4			14	6.9			0.244
Mode of arrival									
Walk-in	110	40.6			85	41.8			
Ambulance	161	59.4			118	58.2			
Arrival time (hour)									
<2	139	51.3			68	33.5			**0.002***
2-6	64	23.6			66	32.5			0.294
6-12	9	3.3			10	4.9			0.426
>12	59	21.8			59	29.1			0.305

SD: Standard deviation; * Statistically significant.

Table 2
The treatment duration, door-to-needle time, and mortality comparison between the periods

Variables	Pre-COVID-19 period (n=271)		COVID-19 period (n=203)		*p*
	n	%	n	%	
Treatment					**0.005***
Very urgent CAG (first 2 h)	238	87.8	194	95.6	
Urgent CAG (2-8 h)	29	10.7	8	3.9	
Thrombolytic	4	1.5	1	0.5	
Door-to-needle time (min)	45		37		0.183
Hospital mortality					0.997
Yes	24	8.8	18	8.8	
No	247	91.2	185	91.2	

CAG: Coronary angiography.

significant disparity in the duration of cardiology consultation subsequent to diagnosis (p=0.855).

The treatments administered to patients with STEMI encompassed very urgent CAG (within a span of 2 h), urgent CAG (spanning from 2 to 8 h), and the application of thrombolytic agents. Out of a total of 474 patients, 432 (91.1%) underwent very urgent CAG, 37 (7.8%) underwent urgent CAG, and a decision concerning thrombolytic therapy was made in five (1.1%) instances.

Upon scrutinizing the treatments administered in the pre-COVID-19 and COVID-19 periods, the frequency of very urgent CAG escalated from 87.8 to 95.6%, whereas urgent CAG experienced a decline from 10.7 to 3.9%. The decision for thrombolytic therapy dwindled from 1.5 to 0.5%. A greater number of very urgent CAG procedures were executed during the COVID-19 period. Patients were admitted to CAG more promptly during the COVID-19 period. A statistical significance was detected between the two periods (p<0.05).

Table 3
Comparison of patient discharges between the pre-COVID-19 and COVID-19 periods

Discharge time	Mean±SD	Min-Max
Pre-COVID-19	5.45±4.026	1-28
COVID-19	5.29±3.807	1-32

COVID-19: Coronavirus disease 2019; SD: Standard deviation.

In the pre-COVID-19 period, the mean door-to-needle time was 51.61±35.32 min. In the COVID-19 period, it was reduced to 49.09±46.59 min.

Within the pre-COVID-19 period, 24 (8.8%) out of 271 patients succumbed. During the COVID-19 period, this figure was 18 (8.8%). No statistically significant disparity was discerned in the evaluation (p=0.997) (Table 2).

When analyzing the duration of hospital stays for patients, specifically comparing the pre-COVID-19 and COVID-19 periods, it was found that the mean duration for the pre-COVID-19 period was 5.45±4.026 days. The shortest stay recorded in this period was one day, while the longest stay lasted for 28 days. The mean duration for the COVID-19 period was 5.29±3.807 days, with a minimum stay of one day and a maximum stay of 32 days. The median durations for both periods were found to be 4 days. Upon comparing the two periods, no statistically significant difference was observed (p=0.655) (Table 3).

DISCUSSION

With the declaration of COVID-19 as a global pandemic, states initially opted to cancel all elective procedures and place emphasis on the importance of staying at home for patients and their families. These measures resulted in a notable reduction in the number of non-COVID-19-related complaints presented to the emergency department. European countries have observed a significant decrease in the incidence of STEMI cases since the onset of

the pandemic, prompting inquiry into the potential factors contributing to this change. A study conducted by the Spanish Society of Cardiology, along with similar findings in Hong Kong, reported a decline of up to 40% in PCI procedures for STEMI.[11]

Our study aimed to examine whether there were any disparities in the emergency management of STEMI patients between the pre-COVID-19 and COVID-19 periods. In our investigation, we found no statistically significant differences in the age and sex distributions of patients who sought care at the emergency department during both the pre-COVID-19 and COVID-19 periods. Similarly, Ayad et al.[12] conducted a study that revealed no significant distinctions in the age and sex of patients between the two periods.

When comparing the timing of STEMI patients' presentations at the emergency department in the pre-COVID-19 and COVID-19 periods, it was observed that during the pre-COVID-19 period, 139 patients arrived within a time frame of less than 2 h, whereas in the COVID-19 period, only 68 patients arrived within the same time frame. Notably, STEMI patients exhibited a significant delay in seeking care at the emergency department during the COVID-19 period. Hammad et al.'s[13] study reported that during the COVID-19 period, 35 patients with STEMI presented themselves 12 h after experiencing symptoms. Furthermore, 27% of these patients refrained from seeking care due to fear of COVID-19, 18% attributed their symptoms to COVID-19, and 9% wished to avoid burdening the emergency department amidst the pandemic. Given the retrospective nature of our study, we were unable to explore the specific reasons for these delays in presentation. However, it is plausible that concerns surrounding infection, movement restrictions, and the desire to minimize the strain on hospitals may have contributed to this situation.[14]

In our investigation, the mean duration from the moment the patient manifested symptoms of STEMI to the time of admission for CAG was found to be 51.61±35.32 min during the pre-COVID-19 era. However, in the COVID-19 era, this time frame was reduced to 49.09±46.59 min. Existing literature has shown that the period for patient admission for CAG has increased during the COVID-19 era compared to the pre-COVID-19 era, as stated in numerous studies.[12,13,15,16] In our research, although no statistically significant outcome was obtained, it was observed that CAG procedures were carried out more expeditiously within our hospital during the COVID-19 era. During this time, patients presenting with STEMI symptoms were admitted for CAG without waiting for polymerase chain reaction (PCR) test results, assuming that each patient had COVID-19. They were then examined and treated according to the latest guidelines. All healthcare professionals in our hospital quickly evaluated the patients while ensuring their own personal safety measures. In our hospital, patients with STEMI who required emergency CAG were taken to the angiography room without waiting for PCR results. In addition, as in the whole world, the number of patients presenting to our hospital during the COVID-19 period decreased compared to the pre-COVID-19 period.[15,16] It was thought that the decrease in the number of presenting patients and the resulting decrease in the workload on healthcare professionals contributed to the shortening of the admission time for CAG during the COVID-19 period.

In our study, the mean time for STEMI patients to be consulted with cardiology after receiving a diagnosis was 15.90±21.97 min. In the study conducted by Duygu[17] in our hospital in 2012, this duration was reported to be an median of 17 min. The relatively shorter consultation times for patients diagnosed with STEMI in our hospital indicate an improvement in the diagnosis process. In our hospital, using current guidelines for the diagnosis and treatment of patients presenting with chest pain and the healthcare personnel's dedication to ensuring personal safety throughout the diagnosis and treatment process were considered significant factors in shortening the diagnosis process. In our study, when treatment decisions were evaluated, statistically significant differences were found in the pre-COVID-19 and COVID-19 periods. In the COVID-19 period, it was thought that not waiting for PCR results by assuming that patients were infected with COVID-19 and taking personal safety measures increased the rate of emergency PCI due to the decrease in the number of patients presenting to the emergency department. Studies recommending delaying CAG or using thrombolytic therapy until the infection status with COVID-19 becomes clear exist in the literature.[18,19] However, in our hospital,

the gold standard treatment for STEMI, which is CAG, was continued to be applied without delay.

In the study conducted by Xiang et al.[14] an increase in mortality was observed during the pandemic period. However, in our study, it was observed that the mortality rates did not change in the pre-COVID-19 and COVID-19 periods. It was thought that the implementation of a standardized diagnosis and treatment process in line with current guidelines and not delaying the CAG procedure were the main reasons for the nonincrease in mortality in our hospital.

The relatively low number of patients in our study, insufficient patient admissions during the COVID-19 pandemic, inability to reach a sufficient number of COVID-19-positive STEMI patients, short-term follow-up of patients, and obtaining patient information from records are important limitations to this study.

In conclusion, a decrease was observed in the number of patients diagnosed with STEMI and the number of admissions within the critical first 2 h after symptom onset due to concerns related to the COVID-19 pandemic. The time taken for patients to be referred to cardiology after being diagnosed with STEMI at our center was not affected by seasonal changes. The door-to-needle time was accomplished in a shorter period during the COVID-19 pandemic. Patients at our center were admitted to the catheterization laboratory at the same speed, regardless of whether it was before or during the pandemic. As a result, this study did not observe any adverse effects of the pandemic period on the emergency management of patients diagnosed with STEMI.

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylül University Faculty of Medicine Ethics Committee (date: 22.02.2021, no: 2021/06-03). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Design, data collection, analysis and writing were made: S.K.; Supervision and critical review were made: F.C.; Materials were made: B.Ş.; Literature review and references were made: A.A.B.

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Relationship between cryptogenic ischemic stroke and P wave peak time

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ABSTRACT

Objectives: This study aimed to examine whether P wave peak time (PWPT), a predictor of atrial fibrillation (AF), is significantly higher at the time of diagnosis in cryptogenic ischemic stroke patients.

Patients and methods: The retrospective was conducted with 118 individuals (72 males, 46 females; mean age: 66.4±13.8 years) with cryptogenic ischemic stroke in the patient group and 118 individuals (77 males, 41 females; mean age: 63.2±16.1 years) without cerebrovascular disease in the control group between January 2021 and December 2023. The groups were compared regarding PWPT.

Results: As a result of multivariate regression analysis, PWPT-D2 and PWPT-V1 were found to be independent predictors of cryptogenic ischemic stroke. In the ROC analysis, when PWPT-D2 was >51.5 msec, the sensitivity for the diagnosis of cryptogenic ischemic stroke was found to be 80%, and the specificity was 76%. When PWPT-V1 was >46 msec, the sensitivity for the diagnosis of cryptogenic ischemic stroke was found to be 75%, and the specificity was 73%.

Conclusion: P wave peak time is an important predictor of cryptogenic ischemic stroke. The reason for the high PWPT level in these patients may be undetected AF. Therefore, longer-term rhythm Holter may be recommended in these patients.

Keywords: Atrial fibrillation, electrocardiography, cryptogenic ischemic stroke, P wave peak time.

Atrial fibrillation (AF) is an important cause of cryptogenic stroke, and if AF is detected in these patients, anticoagulation is required to prevent recurrent strokes.[1] Studies have shown that the use of direct oral anticoagulant therapy in cryptogenic stroke patients is not superior to standard antiplatelet therapy.[2] This shows us the importance of detecting AF in cryptogenic stroke patients. However, the costs and availability of diagnostic devices in daily clinical routine make long-term heart rhythm monitoring challenging.[3] There is a need for simple and applicable diagnostic methods that can predict AF in patients with cryptogenic ischemic stroke where we cannot detect AF in its etiology for these reasons. Related studies have identified features of electrocardiography (ECG), echocardiography, and neuroimaging that are important for the diagnosis of AF in cryptogenic ischemic stroke patients.[4] Additionally, some laboratory biomarkers have been associated with AF in cryptogenic ischemic stroke patients.[5]

P wave parameters and indices derived from these parameters are used for measurements of atrial electrical activity in ECG. Additionally, these parameters and indexes are also used to detect the possibility of AF. Some studies have found that there is a direct correlation between abnormalities in the P wave and P wave-derived parameters and the risk of cerebrovascular events.[6] Parameters such as P wave duration and P wave peak time (PWPT) derived from

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the P wave have been found to be associated with AF and cerebrovascular events.[7]

This study aimed to examine whether PWPT, a predictor of AF, is significantly higher at the time of diagnosis in cryptogenic ischemic stroke patients. If the PWPT duration is significantly higher in cryptogenic ischemic stroke disease, longer follow-up with rhythm Holter may be recommended to detect AF in these patients since PWPT is an important predictive parameter for AF.[7] If AF is detected as a result of prolonged rhythm Holter duration in cryptogenic ischemic stroke patients, anticoagulant therapy could be considered in the treatment of these patients. In this way, mortality and morbidity could decrease in cryptogenic ischemic stroke patients.

PATIENTS AND METHODS

This retrospective study was conducted with 118 patients as patient group (72 males, 46 females; mean age: 66.4±13.8 years) with cryptogenic ischemic stroke at the Uşak University Training and Research Hospital between January 2021 and December 2023. In the control group, 118 patients (77 males, 41 females; mean age: 63.2±16.1 years) with similar baseline characteristics and without cerebrovascular disease were included. The patients were diagnosed with cryptogenic ischemic stroke by neurologists using radiological imaging. Patients with cryptogenic ischemic stroke were monitored with rhythm Holter for 72 h from the moment of diagnosis. Patients with previous cerebrovascular disease, patients with a history of AF, patients with pacemakers, patients with active infection, patients whose ECG was AF when diagnosed with cryptogenic ischemic stroke, patients with AF detected as a result of 72-h rhythm Holter after the diagnosis of ischemic stroke, patients with moderate and severe heart valve disease, patients with chronic renal failure, patients with congenital heart disease, patients with heart failure, patients with carotid artery disease, patients with hematological diseases, patients with rheumatological disease, and patients who did not have an ECG at the time of diagnosis were excluded from the study.

Electrocardiography at the time of diagnosis was transferred to digital media. P wave peak times were calculated and defined as the time from the beginning to the peak of the P wave, calculated from leads D2 and V1 (Figure 1). Electrocardiography parameters, echocardiography parameters, and blood parameters at the time of diagnosis were compared between the groups.

Statistical analysis

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Histograms, the Shapiro-Wilk test, and q-q plots were used to understand whether the data were normally distributed. The Mann-Whitney U and T tests were applied to compare variables between the groups. The chi-square test was used for categorical variables. Logistic regression analysis was used to identify risk

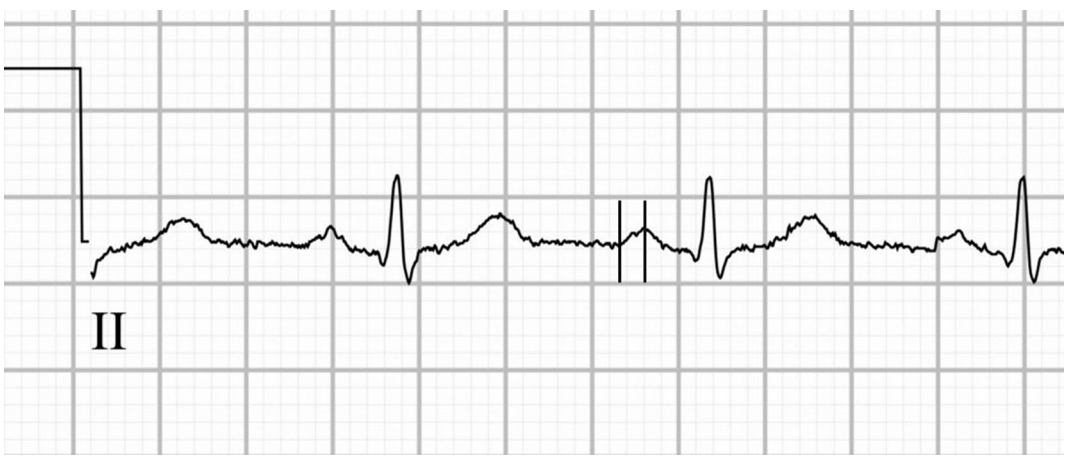

Figure 1. Calculation of PWPT-D2.
PWPT: P wave peak time.

factors affecting cryptogenic ischemic stroke. Variables found to be statistically significant as a result of logistic regression analysis were evaluated in multivariate logistic regression analysis. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance power of PWPT in lead D2 (PWPT-D2) and PWPT in lead V1 (PWPT-V1) in cryptogenic ischemic stroke disease. The area under the curve, cutoff value, sensitivity, and specificity were calculated for both parameters. The statistical significance level was accepted as $p<0.05$.

RESULTS

No cause of stroke was found in any of the 118 patients with cryptogenic ischemic stroke included in the study. As a result of comparing the variables in the patient and control groups, PWPT-D2 duration (58.9±9.8 and 48.4±7.6, respectively; $p<0.001$) and PWPT-V1 duration (56.9±8 and 47.5±8.7, respectively; $p<0.001$) were longer in patients with cryptogenic ischemic stroke. There was no significant difference between the two

Table 1
Comparison of variables between the groups

	Patient group (n=118)			Control group (n=118)			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			66.4±13.8			63.2±16.1	0.14
Sex							
Female	46	38.9		41	34.7		0.47
Diabetes mellitus	50	42.3		45	38.1		0.08
Hypertension	69	58.4		63	53.5		0.07
Hyperlipidemia	48	40.6		45	38.1		0.34
CAD	31	26.2		24	20.3		0.06
Body mass index (kg/m^2)			26.3±3.7			25.9±3.6	0.53
PWPT-D2 (msec)			58.9±9.8			48.4±7.6	**<0.001**
PWPT-V1 (msec)			56.9±8			47.5±8.7	**<0.001**
Heart rate (per min)			81±9.7			79±8.2	0.41
Ejection fraction (%)			57.9±8.1			58.9±7.4	0.36
Left atrium diameter (mm)			38.2±5.8			37±5.9	0.15
White blood cell (10^3/uL)			8.8±3			8.3±2.9	0.28
Neutrophil (10^3/uL)			67.5±10.5			66.1±11.1	0.36
Lymphocyte (10^3/uL)			23.1±9.2			22.1±7.9	0.41
Hemoglobin (g/dL)			12.9±1.9			13.2±1.4	0.18
Platelet (10^3/uL)			252.5±89.8			257.2±82.8	0.27
Blood urea nitrogen (mg/dL)			37.7±14.8			36.1±16	0.45
Creatinine (mg/dL)			0.95±0.45			0.86±0.19	0.08
Sodium (mEq/L)			138.7±2.7			139.2±2.6	0.13
Potassium (mEq/L)			4.2±0.46			4.1±0.41	0.15
Glomerular filtration rate (mL/min)			81.3±25.7			83.7±24.7	0.50
Total cholesterol (mg/dL)			190.3±57.9			177.6±73.4	0.18
Triglyceride (mg/dL)			184.4±120.8			174.8±123.8	0.58
High density lipoprotein (mg/dL)			44.1±14.5			45.2±14.4	0.61
Low density lipoprotein (mg/dL)			105.1±37.9			102.9±38.8	0.69

SD: Standard deviation; CAD: Coronary artery disease; PWPT: P wave peak time.

Table 2
Univariate and multivariate logistic regression analysis

	Univariate			Multivariate		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
PWPT-D2	1.156	1.103-1.212	**<0.001**	1.131	1.073-1.192	**<0.001**
PWPT-V1	1.132	1.089-1.177	**<0.001**	1.101	1.046-1.159	**<0.001**
Hypertension	1.462	0.947-2.112	0.10			
Diabetes mellitus	1.065	0.933-1.179	0.09			
Coronary artery disease.	1.013	0.912-1.213	0.07			
Hyperlipidemia	1.009	0.978-1.013	0.40			

OR: Odds ratio; CI; confidence interval; PWPT: P wave peak time.

groups in any parameter except for PWPT-D2 and PWPT-V1 (Table 1).

Regression analysis was performed to find parameters predictive of cryptogenic ischemic stroke. Coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, PWPT-D2, and PWPT-V1 were included in the univariate regression analysis. As a result of the multivariate regression analysis, PWPT-D2 and PWPT-V1 were found to be independent predictors of cryptogenic ischemic stroke (Table 2).

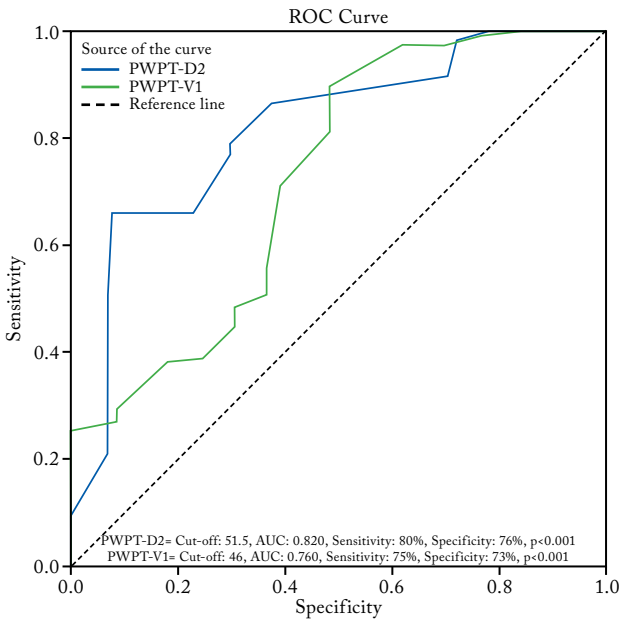

Figure 2. Receiver operating characteristic curve analysis for PWPT-D2 and PWPT-V1.
PWPT: P wave peak time.

In the ROC analysis, when PWPT-D2 was >51.5 msec, the sensitivity for the diagnosis of cryptogenic ischemic stroke was found to be 80%, and the specificity was 76%. When PWPT-V1 was >46 msec, the sensitivity for the diagnosis of cryptogenic ischemic stroke was found to be 75%, and the specificity was 73% (Figure 2).

DISCUSSION

This study helps elucidate the etiology of cryptogenic ischemic stroke. As a result of our study, we found that PWPT, which is a strong predictor of AF, was significantly higher in cryptogenic ischemic stroke patients at the time of diagnosis. This suggests that the cause of cryptogenic ischemic stroke disease is undetected AF.

Atrial fibrillation significantly increases the risk of ischemic stroke in patients.[8] Atrial fibrillation is known at the time of diagnosis in approximately 15 to 18% of patients with ischemic stroke or transient ischemic attack.[9] Therefore, the cause of stroke in the majority of these patients is AF.[9] In another study, it was found that 30% of patients who were diagnosed with AF before their stroke diagnosis also had AF when they were admitted to the hospital.[10] In the same study, it was found that 4 to 13% of patients whose AF diagnosis was unknown at the time of stroke had AF attacks during their follow-up.[10] In another study conducted independently of these, it was found that the first AF attack was detected in the ECGs taken at the time of diagnosis in 1.7 to 16% of patients with acute ischemic stroke or transient ischemic attack.[11] In the same study, the first AF attack was

detected in approximately 0.2 to 13% of all patients as a result of rhythm monitoring with an extra 24-h ECG.[11] In 72-h ECG rhythm monitoring, the first AF attack was detected in approximately 2.3 to 11% of ischemic stroke patients.[11] After rhythm monitoring with ECG for one week after stroke diagnosis, AF was diagnosed in 1.7 to 14% of all patients.[11] In a randomized controlled study conducted with stroke patients, the first AF attack was detected in 18 of 200 patients with 10-day rhythm Holter monitoring.[12] In the 10-day rhythm Holter follow-up performed after a three-month interval, the first AF attack was detected in 10 patients.[12] In the 10-day rhythm Holter follow-up performed after a six-month interval, AF was not found in any of the remaining stroke patients.[12] In a study conducted with patients diagnosed with cryptogenic ischemic stroke, the first AF attack was detected in 46 of 286 patients after rhythm monitoring for 30 days.[13] All this suggests that a new method is needed to find AF in patients with cryptogenic ischemic stroke. In our study, the prolonged detection of PWPT, which is a predictor of AF, in cryptogenic ischemic stroke patients should suggest AF. Patients with long PWPT should be evaluated for anticoagulant use. In addition, long-term and frequently intermittent rhythm Holter should be recommended to these patients. Already, the USA guideline recommends rhythm monitoring with ECG for 30 days to detect AF in patients diagnosed with cryptogenic ischemic stroke (Class 2A, Level C).[14] The European Society of Cardiology recommends rhythm monitoring with ECG to detect AF for at least 72 h from the moment of diagnosis in patients who have had a stroke or transient ischemic attack but do not have known AF (Class 1, Level B).[15] In our study, we fitted patients with a rhythm Holter to detect AF for 72 h from the stroke diagnosis. However, we did not find AF in any patient. In the European Stroke Organization guideline, it is recommended that rhythm monitoring be performed for a long time in stroke patients with the possibility of AF, but there is no information about the duration in acute strokes.[16]

Cryptogenic ischemic stroke accounts for one-quarter of ischemic strokes.[17] Cryptogenic ischemic stroke is more likely to be a recurrent stroke than other strokes. The probability of recurrence of ischemic stroke in these patients is between 3 and 6%.[18] Studies suggest new clinical scores in cryptogenic stroke patients with no etiology detected.[19] Although previous studies on this subject suggested long-term heart rhythm monitoring with implantable devices in cryptogenic stroke patients, this cannot be fully implemented.[20] Since the required effort and cost are quite high, the probability of being diagnosed with AF in this patient group in one year is approximately 10%.[20]

This supports the need to determine the etiology in patients with cryptogenic ischemic stroke. Although various risk factors for AF have been identified in previous studies, the use of a single predictor may not be sufficient to detect AF in patients according to large population-based studies.[21] For this reason, risk scores based on imaging, clinical evaluation, and echocardiographic features have been developed to detect AF in patients.[21] Although these scores provide important results for AF, such scores have not been developed in cryptogenic ischemic stroke patients.[21]

In a study, PWPT-D2 was found to be a significant predictor of paroxysmal AF in acute ischemic stroke patients.[22] The P wave shows us the conduction time between the sinoatrial node and the atrioventricular node.[22] There is restructuring in the atria in paroxysmal AF patients.[22] In addition, abnormal activities in the atria may cause changes in the structure of the atrium and affect the electrophysiological mechanism.[23] These changes can make significant changes on the P wave.[23] P wave parameters were found to predict poor clinical outcomes, such as AF, cerebrovascular accident, death, and heart failure.[24] P wave peak time is an important ECG parameter that is the subject of many articles.[22] In a study conducted on patients with coronary artery disease, a significant correlation was found between left atrial dysfunction and PWPT.[25] Additionally, in another study, it was found that the disease severity increased as the PWPT-D2 duration increased in coronary artery patients admitted with the diagnosis of non-ST-elevation myocardial infarction.[26] In addition to these published studies, another study conducted with hypertensive patients observed that left ventricular end-diastolic pressure increased as PWPT-D2 duration increased.[27] In a study investigating the relationship between silent ischemic stroke and PWPT, it was found that longer PWPT in leads D2 and V1 was associated with silent ischemic stroke, while PWPT-D2 was independently

associated with silent ischemic stroke.[23] In our study, PWPT-D2 and PWPT-V1 were found to be higher in the cryptogenic ischemic stroke patient group. Additionally, these two parameters were found to be independent predictors in the diagnosis of cryptogenic ischemic stroke.

Cardioembolic conditions constitute 25% of total ischemic strokes.[28] Cardioembolic strokes are associated with worse prognosis than noncardioembolic strokes.[29] Since the cause of the stroke in cryptogenic ischemic stroke patients is not identified, it is unclear whether there is a cardioembolic cause. However, as a result of our study, we detected PWPT prolongation in these patients and revealed the possibility of undetected AF in the etiology of cryptogenic ischemic stroke. In ischemic stroke patients, as the cardiovascular risk status increases and the ECG follow-up period increases, the probability of detecting AF also increases.[30] In our study, the rates of hypertension, coronary artery disease, hyperlipidemia, and diabetes mellitus were higher in the group with cryptogenic ischemic stroke, but there was no statistical difference compared to the other group. This situation may have caused the PWPT period to extend slightly. Prospective randomized controlled studies are needed to better understand this issue.

The main limitation of this study is the retrospective design. Multicenter studies with a large number of participants are needed to better understand whether PWPT detects AF in etiology in patients with cryptogenic ischemic stroke. To determine whether PWPT truly detects undetectable AF in cryptogenic ischemic stroke patients, it needs to be compared with a group of patients with ischemic strokes of different etiology other than AF, in addition to the existing control group. This situation creates a different limitation that is important for our study. Additionally, there was not enough follow-up time to detect AF in the patients. The inability to wear a rhythm Holter for longer than 72 h is also among the major limitations.

In conclusion, the high PWPT in patients with cryptogenic ischemic stroke of unknown etiology suggests that these patients have undetected AF in their etiology. Therefore, anticoagulant treatment may be considered in these patients to prevent recurrent strokes. Additionally, long-term rhythm Holter may be considered to detect AF in these patients.

Ethics Committee Approval: The study protocol was approved by the Uşak University Training and Research Hospital Ethics Committee (date: 06.01.2021, no: E-38824465-020-2221). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Cardiovascular Surgery and Interventions

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Evaluation of alveolar-capillary membrane functions by thoracic ultrasonography in heart failure

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ABSTRACT

Objectives: This study aimed to research the effect of the increased B-line count (interstitial fluid accumulation) in patients with congestive heart failure on the diffusion capacity of the alveolar-capillary membrane.

Patients and methods: This prospective study was conducted with 77 inpatients diagnosed with pulmonary edema and decompensated heart failure between January 2018 and December 2018. The B-line counts of the patients were calculated through echocardiography and thoracic ultrasonography within the first 24 h of their admission, and the patients were categorized into two groups based on their B-line counts being <15 (n=26; 18 males, 8 females; mean age: 48.6±3.3 years; range, 21 to 72 years) or >15 (n=51; 36 males, 15 females; mean age: 53.7±2.0 years; range, 20 to 79 years). After sufficient diuretic treatment, the patients who were able to tolerate and pass the tests were then subjected to a respiratory function test, diffusion test [DLCO (diffusing capacity of the lungs for carbon monoxide)], and six-minute walk test (6MWT).

Results: The following results in study were found in the echocardiography of the patients with a B-line number >15: lower right ventricular ejection fraction (p=0.003), lower right ventricular systolic motion (p=0.014), higher systolic pulmonary artery pressure (p<0.0001), higher tricuspid regurgitant velocity (p=0.001), more dilated vena cava inferior radius (p<0.0001), higher left atrium volume (p=0.007), higher early diastolic transmitral flow velocity/early diastolic mitral anullar velocity (E/e´) >15 (p<0.0001), and higher pleural effusion (p=0.014). The following results were found in the respiratory function test, DLCO test, and 6MWT of the patients with a B-line number >15: lower forced vital capacity (p<0.0001), lower forced expiratory volume in 1 sec (p=0.002), lower corrected DLCO (p<0.0001), lower 6MWT (p<0.0001).

Conclusion: B-line counts >15 may be a predictor of a decrease in diffusion capacity, restrictive pattern in respiratory function, decrease in right ventricular function, and increase in pulmonary vascular resistance.

Keywords: Alveolar-capillary membrane, heart failure, thoracic ultrasonography.

Heart failure is a cardiac structural or functional disorder that causes the heart to fail to provide enough oxygen to meet tissues' metabolic needs.[1] Pulmonary edema is the accumulation of fluid in the interstitium and alveoli due to increased pulmonary capillary pressure. Thoracic ultrasonography is one of the methods used in addition to methods such as chest radiography and computed tomography to evaluate this accumulated fluid.[2] B-line pulmonary edema evaluated by thoracic ultrasonography is a portable, nonradiating, and useful noninvasive method.[3-11]

In heart failure, as a result of the development of pulmonary edema, the interstitial tissue of the alveolar-capillary membrane starts to increase; in other words, the extracellular matrix and the thickness of the alveolar-capillary membrane increase due to the increased capillary pressure and the continuous physical stress caused by the increased capillary volume. This situation causes a decrease in gas diffusion.[12-16] The test evaluating alveolar-capillary membrane permeability is the lung diffusion test, which measures the diffusing capacity of the lungs for carbon monoxide (DLCO). The diffusion test is

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defined as the carbon monoxide uptake rate in mL at 1 min and each mmHg driving pressure, expressed as mL/min/mmHg. An increase in alveolar-capillary membrane thickness and, consequently, decrease in gas diffusion may be one of the predictors of increased mortality in heart failure.

The purpose of our study was to compare the results of B-line count and diffusion test with thoracic ultrasonography in patients with heart failure and to examine the effect of increasing the number of B-lines (interstitial fluid accumulation) on alveolar-capillary membrane diffusion capacity. Furthermore, the study aimed to examine the pulmonary vascular resistance, pulmonary artery pressure, and right ventricular effect due to remodeling in patients with high B-line burden and less DLCO.

PATIENTS AND METHODS

The prospective study was conducted with 77 patients hospitalized due to an acute heart failure diagnosis in the cardiology department of the Ege University Medical Faculty Hospital between January 2018 and December 2018. In the first 24 h after diuretic treatment initiation following the patients' hospitalization, echocardiography data and B-line count by thoracic ultrasonography were recorded. According to the results of thoracic ultrasonography of the patients and the number of B-lines, the patients were divided into two groups: those with <15 B-lines (n=26; 18 males, 8 females; mean age: 48.6±3.3 years; range, 21 to 72 years) and those with >15 B-lines (n=51; 36 males, 15 females; mean age: 53.7±2.0 years; range, 20 to 79 years). The presence of left ventricular ejection fraction >40%, age below 18 and over 80, patients with congenital heart disease, patients who could not undergo optimal echocardiographic examination due to limited echogenicity, patients with a diagnosis of malignancy, patients with severe valve stenosis, and severe chronic disease patients diagnosed with obstructive pulmonary disease and pneumonia were excluded from the study.

After the diuretic treatment was administered to the patients, they were evaluated with a visual analog dyspnea scale and bedside dyspnea test. Patients who did not define dyspnea on the visual analog dyspnea scale and who did not develop dyspnea in the bedside dyspnea test were considered compensated, and the patients who could tolerate the test and did not have contraindications underwent a pulmonary function test, diffusion test, and 6-minute walk test (6-MWT).

Among 77 heart failure patients included in the study, right heart catheterization was applied to the patients deemed necessary to evaluate their suitability for left ventricular support therapy and heart transplantation, and peak oxygen uptake (pVO_2) was calculated with metabolic tests. The pulmonary function test results, DLCO, 6-MWT results, echocardiography parameters, right catheterization findings, and pVO_2 values were compared between the groups.

Thoracic ultrasonography was performed with GE Healthcare Vivid E9 M5S probe (1.5-4.5 MHz; GE Healthcare Technologies Inc., Chicago, IL, USA) during the first 24 h of hospitalization in the patients included in the study. While evaluating by thoracic ultrasonography, the B-line number was calculated using the method of eight lung zones or four regions for each hemithorax.[10,11] After the B-line number in each region was added together, the patients were divided into two groups, as described above. The presence of pleural effusion was determined during the evaluation with thoracic ultrasonography.

Statistical analysis

Data were analyzed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as numbers and percentages for categorical variables and mean and standard deviation for numerical variables. The Kolmogorov-Smirnov test was used to test whether the variables were normally distributed. Student's t-test was used to compare numerical variables with normal distribution between matched groups, and the Wilcoxon test was used to compare numerical variables that did not show normal distribution. Student's t-test was used to compare quantitative data with normal distribution, and the chi-square test was used to compare qualitative data. While the arithmetic means and standard deviation were presented for numerical variables with normal distribution, median and interquartile range values were shown for those that did not show normal distribution. Pearson's correlation test was used in correlation analysis. A p-value <0.05 was considered statistically significant.

RESULTS

Those with a B-line number <15 had a mean body mass index of 27.9±1.09 kg/m^2), whereas

those with a B-line number >15 had a mean body mass index of 28.2±0.55 kg/m^2). In the comparison between the group with the B-line <15 (30% ischemic cardiomyopathy, 69% nonischemic cardiomyopathy, 50% hypertension, 42% diabetes mellitus (DM), 30% atrial fibrillation, and 3% chronic renal failure) and the group with a B-line number >15 (51% ischemic cardiomyopathy, 49% nonischemic cardiomyopathy, 62% hypertension, 41% DM, 37% atrial fibrillation, and 13% chronic renal failure), no significant difference was found in terms of demographic characteristics and comorbid diseases. No significant difference was observed between the group with a B-line <15 (69% ACE [angiotensin-converting enzyme] inhibitor, 19% ARB [angiotensin receptor blocker], 96% beta-blocker, 69% MRA [mineralocorticoid receptor antagonist], 3% ARNI [angiotensin receptor/neprilysin inhibitor], 7% ivabradine, 19% digoxin use history, 7% CRT-D [cardiac resynchronization therapy with defibrillator] implantation) and the group with >15 B-lines (52% ACE inhibitor, 11% ARB, 92% beta-blocker, 64% MRA, 3% ARNI, 13% ivabradine, 13% digoxin use history and 15% CRT-D) in terms of the drugs used by the patients and the treatment applied.

Considering the echocardiography findings performed within the first 24 h after hospitalization in terms of left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrium (LA), and left ventricular end-systolic volume (LVESV) values, no statistically significant difference was found between the group with <15 B-lines (LVEF, 26±0.7%; LVEDD, 6.6±0.16 cm; LVESD, 5.4±0.21 cm; LA, 4.6±0.15 cm; LVESV, 181±13.9 mL) and the group with >15 B-lines (LVEF, 25±0.6%; LVEDD, 6.4±0.12 cm; LVESD, 5.27±0.15 cm; LA, 4.9±0.10 cm; LVESV, 156±7.8 mL).

When the groups with <15 B-lines right ventricular ejection fraction (RVEF), 49±2.06%; ratio of patients with early diastolic transmitral flow velocity/early diastolic mitral anullar velocity (E/e´) >15, 15.4%; LA volume, 29.7±1.09 mL; right ventricular systolic motion (RVSm), 8.9±0.44; tricuspid regurgitant velocity (TRV), 2.8±0.06 m/sec; systolic pulmonary artery pressure (SPAP), 3.08±1.9 mmHg; vena cava inferior (VCI) diameter, 2.08±0.05 cm) and >15 B-lines (RVEF, 41±1.4%; ratio of patients with E/e´ >15%, 62.72%; LA volume, 33.2±0.7 mL; RVSm, 7.5±0.28; TRV, 3.22±0.05 m/sec; SPAP, 55.08±1.4 mmHg; VCI diameter, 2.39±0.03 cm) were compared, RVEF was lower (p=0.003) and the E/e´ ratio was higher in the group with >15 B-lines (p<0.0001). Higher LA volume (p=0.007), lower RVSm (p=0.014), higher TRV (p=0.001), higher SPAP (p<0.0001), and larger VCI diameter (p<0.0001) were determined in the >15 B lines group (Table 1).

When the group with <15 B-lines 15 (30.8% mild tricuspid insufficiency, 61.5% moderate tricuspid insufficiency, 7.7% severe tricuspid insufficiency, 7.7% without mitral insufficiency, 23.1% mild mitral insufficiency, 53.8% moderate mitral insufficiency, and 11.5% severe mitral insufficiencies) and the group with >15 B-lines (11.8% mild tricuspid insufficiency, 64.7% moderate tricuspid insufficiency, 23.5% severe tricuspid insufficiency, 2% without mitral

Table 1
Patients' echocardiography findings evaluated in the first 24 h after hospitalization

Echocardiographic findings	B line <15 (n=26)	B line >15 (n=51)	
	Mean±SD	Mean±SD	*p*
LVEF (%)	26±0.7	25±0.6	0.185
LVEDD (cm)	6.6±0.16	6.4±0.12	0.130
LVESD (cm)	5.4±0.21	5.27±0.15	0.255
LA (cm)	4.6±0.15	4.9±0.10	0.138
LVEDV (mL)	248± 17.5	209±9.4	0.041
LVESV (mL)	181± 13.9	156±7.8	0.143

SD: Standard deviation; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; LA: Left atrium; LVEDV: Left ventricular end- diastolic volume; LVESV: Left ventricular end-systolic volume.

insufficiency, 7.8% mild mitral insufficiency, 54.9% moderate mitral insufficiency, and 35.3% severe mitral insufficiencies) were compared, no statistically significant difference was observed in terms of tricuspid valve insufficiency, and it was found that the mitral valve insufficiency was more frequent in the group with >15 B-lines (p=0.043, Table 2).

While there was no patient with pleural effusion in thoracic ultrasonography in the group with <15 B-lines, the rate of patients with pleural effusion in the group with >15 B-lines was 19.6%. When the two groups were compared, pleural effusion was observed more frequently in thoracic ultrasonography in the group with >15 B-lines (p=0.014, Table 2).

Table 2
Patients' echocardiography findings evaluated in the first 24 h after hospitalization, and thoracic ultrasonographic findings evaluated in terms of pleural effusion

	B Line <15 (n=26)			B Line >15 (n=51)			
Echocardiographic findings	n	%	Mean±SD	n	%	Mean±SD	*p*
RVEF %			49±2.06			41±1.4	0.003
Number of patients with E/e'>15	4	15.4		32	62.7		<0.0001
Left atrium volume (mL)			29.7±1.09			33.2±0.7	0.007
RVSm			8.9±0.44			7.5±0.28	0.014
TRV (m/sec)			2.88±0.06			3.22±0.05	0.001
SPAP (mmHg)			43.08±1.9			55.08±1.4	<0.0001
VCI diameter (cm)			2.08±0.05			2.39±0.03	<0.0001
Mitral insufficiency							0.043
No	2	7.7		1	2		
Mild	6	23.1		4	7.8		
Moderate	14	53.8		28	54.9		
Severe	3	11.5		18	35.3		
Number of patients with pleural effusion, detected by thoracic ultrasonography	0	0		10	19.6		0.014

SD: Standard deviation; RVEF: Right ventricular ejection fraction; RVSm: Right ventricular systolic motion; TRV: Tricuspid regurgitant velocity; SPAP: Systolic pulmonary artery pressure; VCI: Vena cava inferior.

Table 3
Comparison of the results of the respiratory function test, DLCO, and six-min walk test between the two groups after diuretic treatment

	B Line <15 (n=26)	B Line >15 (n=51)	
Respiratory function test and DLCO	Mean±SD	Mean±SD	*p*
FVC (%)	78.8±2.86	69.6±1.93	0.008
FVC (L)	3320±169.3	2507±115	<0.0001
FEV1 (%)	76.1±3.02	67.7±2.24	0.036
FEV1 (L)	2664±162.7	2010±106.4	0.002
FEV1/FVC (%)	93.5±2.45	95.6±1.79	0.755
PEF (%)	62.48±3.75	58.8±2.94	0.346
DLCO (mL/mmHg/min)	74.6±1.69	53.5±1.1	<0.0001
cDLCO (mL/mmHg/min)	72.7±1.95	49.8±1.39	<0.0001
Six-minute walk test (meters)	372.6±14.6	220.6±10.5	<0.0001

DLCO: Diffusion test; SD: Standard deviation; FVC: Forced vital capacity; FEV1: Forced expiratory volume during the first seconds; PEF: Peak expiratory flow; cDLCO: Corrected diffusion test.

When the results of respiratory function tests and diffusion test performed after compensation after adequate diuresis were considered, there was no significant difference in forced expiratory volume in 1 sec (FEV1)/forced vital capacity (FVC) and peak expiratory flow (PEF) values between the group with <15 B-lines (FVC, 78.8%±2.86; FVC liter value, 3320±169.3 L; FEV1 percentage value, 76.1±3.02%; FEV1 liter value, 2664±162.7 L; FEV1/FVC ratio, 93%, 5±2.45; PEF, 62.48±3.75%; DLCO, 74.6±1.69 mL/mmHg/min; hemoglobin- and sex-corrected DLCO [cDLCO], 72.7±1.95 mL/mmHg/min) and the group with >15 B-lines (FVC, 69.6%±1.93; FVC liter value, 2507±115 L; FEV1 percentage value, 67.7±2.24%; FEV1 liter value, 2010±106.4 L; FEV1/FVC ratio, 95.6±1.79%; PEF, 58.8±2.94%; DLCO, 53.5±1.1 mL/mmHg/min, cDLCO, 49.8±1.39 mL/mmHg/min). In the group with >15 B-lines, the FVC percentage value was lower ($p=0.008$), the FVC liter value was lower ($p<0.0001$), the FEV1 percentage value was lower ($p=0.036$), the FEV1 liter value was lower ($p=0.002$), the DLCO value was lower ($p<0.0001$), and the cDLCO value was lower ($p<0.0001$). When the group with <15 B-lines (372.6±14.6 m) and >15 B-lines (220.6±10.5 m) were compared, it was observed that the 6-MWT result was lower in the group with >15 B-lines ($p<0.0001$, Table 3).

DISCUSSION

Today, heart failure incidence has increased, and the lifetime risk of developing heart failure reaches up to 20%. Despite the increasing variety of treatments for heart failure, it is still a disease with high mortality.[17] Heart failure mortality determinants are metabolic test (pVO_2), 6-MWT, kidney function tests, N-terminal pro–B-type natriuretic peptide (NT-pro BNP) value, and right ventricular functions. In the latest studies conducted, it is thought that the results of respiratory function tests and diffusion tests may also be determinants of heart failure mortality.

The most important reason for both outpatient clinic admissions and hospitalizations of heart failure patients is dyspnea due to pulmonary edema. To evaluate the patients in terms of pulmonary edema, thoracic ultrasonography, B-line count, and pleural effusion were also added to examinations, such as physical examination findings and chest radiography.

In chronic heart failure, alveolar-capillary membrane changes due to hemodynamic stress caused by increased capillary pressure and changes on the alveolocapillary membrane are irreversible and result in remodeling. Neurohumoral activation due to physical stress caused by increased pulmonary capillary pressure and a decrease in cardiac output stimulates mesenchymal cells and fibrocytes in the interstitium and causes myofibroblasts to proliferate and differentiate. With myofibroblast proliferation, the amount of elastin and collagen begins to increase in the interstitial tissue of the alveolar-capillary membrane, that is, in the extracellular matrix. There is an increase in type 4 collagen and alveolar-capillary membrane thickness. Alveolar-capillary membrane thickening positively reduces pulmonary edema formation; therefore, it protects against increased fluid permeability. However, it causes a decrease in gas diffusion and the formation of restrictive lung syndrome due to increased stiffness, contributing to the development of pulmonary hypertension and a decrease in exercise tolerance. Due to alveolar-capillary membrane thickening, there is a decrease in diffusing capacity in patients with heart failure and a decrease in FVC (restrictive pattern), even if FEV1/FVC is normal. It is thought that the current situation may be the predictor of mortality.[12-16]

In the study conducted by Van Iterson et al.,[18] patients with low DLCO results were found to have lower pVO_2 values in the metabolic test result. As a result of the study, it was observed that there was a decrease in the diffusing capacity of patients with moderate and severe heart failure, and the result of DLCO could be a predictor of mortality, similar to pVO_2, in heart failure patients. In our study, DLCO was found to be lower in the group with >15 B-lines, and >15 B-lines may be a determinant of mortality, similar to DLCO and pVO_2.

Puri et al.[19] administered 10 mL/kg/min 0.9% saline to 10 patients with heart failure, and when the diffusion test results were performed 1 h after the infusion, it was found that the results of alveolar-capillary membrane conductance, FEV1, and peak expiratory flow rates (PEFR) decreased. A saline infusion was given to the patients in the healthy control group, and no change was detected in the respiratory function test and diffusion test performed 1 h later.

Similar results were obtained in our study, and it was observed that the results of DLCO, FVC, and FEV1 were lower in those with >15 B-lines (extravascular fluid retention in the lung). It was observed that the results of DLCO, FVC, and FEV1 might be lower as a result of the increase in alveolar-capillary membrane thickness due to hemodynamic stress caused by excessive extravascular fluid retention.

When another study of Puri et al.[20] was examined, alveolar-capillary membrane diffusive capasity, DLCO, and alveolar volume decreased in the group with heart failure compared to healthy individuals. Although healthy individuals were not included in our study, it is thought that patients with >15 B-lines may have had increased alveolar-capillary membrane thickness, and as a result, DLCO was found to be lower due to decreased permeability.

Morosin et al.[21] found that pVO_2, FEV1, and FVC were lower in the group with DLCO <80% compared to those with DLCO >80% in patients with stable heart failure. Similarly, in our study, FVC and FEV1 were low together with DLCO in the group with >15 B-lines.

Melenovsky et al.[22] included 186 heart failure patients and 21 healthy control group patients in their study. Pulmonary radiographs of heart failure patients were interpreted and grouped as the wet lung group with a congestion score index >0.5 (n=74) and the dry lung group with a congestion index score <0.5 (n=112). Right catheterization, respiratory function tests, diffusion tests, and echocardiography were applied to the wet and dry lung groups. When all findings were compared between the two groups, FVC and DLCO were lower in the heart failure group with wet lungs. When the two groups were compared in terms of FEV1/FVC, it was found that there was no significant difference. Furthermore, in the heart failure group with wet lungs, pulmonary artery compliance was lower, pulmonary vascular resistance and pulmonary stub pressures were higher, right ventricular functions were lower, DLCO results were lower, and a restrictive pattern was observed in the pulmonary function test. In their median follow-up of 333 (interquartile range 80-875) days, it was shown that mortality increased in the wet lung group. In our study, in the group with >15 B-lines, right ventricular functions were found to be lower, DLCO was lower, pulmonary vascular resistance was higher, and a restrictive pattern was observed due to the pulmonary function test. It was observed that there is a significant correlation between the results of our study and the results of the study conducted by Melenovsky et al.[22]

In the study conducted by Coiro et al.,[23] it was determined that the patient group with >30 B-lines had higher mortality, and hospitalization was more frequent as a result of thoracic ultrasonography performed before discharge in heart failure patients. In our study, follow-up could not be performed with mortality and rehospitalization, but in the group with >15 B-lines, DLCO was lower, right ventricular functions were higher, the rate of patients with E/e´ >15% was higher, VCI diameter was more dilated, and pulmonary vascular resistance pressure was higher. These findings are accepted as an indicator of a poor prognosis.

In the CHAMPION study, a device that can measure pulmonary artery pressure with CardioMEMS was evaluated by implanting. In the device follow-up, it was observed that the mean pulmonary artery and pulmonary stub pressure increased during the process from dry lung to pulmonary edema, and if the pulmonary edema picture increased more in the follow-up of DLCO followed by FVC, FEV1/FVC decreased.[24] In our study, DLCO and FVC were low in patients with >15 B-lines (pulmonary edema), but FEV1/FVC decreased.

In the study conducted by Platz et al.,[25] thoracic ultrasonography was examined by an eight-region scanning method before discharge in heart failure patients. It was observed that patients with >3 B-lines had higher mortality and rehospitalization rates. In our study, mortality was not calculated, but in the group with >15 B-lines, the right ventricular function was found to be more suppressed, DLCO was lower, and pulmonary vascular resistance was higher, which could be a predictor of mortality.

In the study by Agostoni et al.,[16] heart failure patients were subjected to metabolic testing and grouped as <12, 12-16, and 16-20 according to the pVO_2 results. In the group with pVO_2 <12, DLCO, alveolar volume, capillary volume, and alveolar-capillary membrane diffusive capasity were lower than in the other groups. Similarly, in our study, the 6-MWT, performed to evaluate functional capacity, and the DLCO were lower in the group with >15 B-lines.

There are some limitations to this study. Short- and long-term follow-up of the patients after discharge from the hospital in terms of mortality and rehospitalization frequency would have been beneficial to the study. Identifying the effect of a B-line number >15 on mortality and hospitalization frequency could support the study results. Although it was not included in our study's method, a higher number of patients who underwent right heart catheterization and had measured right atrial pressure/left atrial pressure, pulmonary arterial pressure, and pulmonary vascular resistance values could contribute to the study. Checking the number of B-lines by thoracic ultrasonography during diffusion tests and before discharge could provide the accuracy of the study results and a better determination of the congestion status of the patients.

In conclusion, a B-line number >15 alone may be predictive in terms of decreased diffusion capacity, decreased right ventricular function, increased pulmonary vascular resistance, and restrictive pattern in respiratory function. There are poor prognosis indicators, such as a 6-MWT and right ventricular function for heart failure. In the group with a B-line number >15, decreased DLCO as a result of decreased six-min walking capacity, more pressure on right ventricular functions, and lower follow-up DLCO suggests that it may be an indicator of poor prognosis in heart failure.

Ethics Committee Approval: The study protocol was approved by the Ege University Faculty of Medicine Ethics Committee (date: January-December 2018, no: 18-2.1/31). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Assessing in-hospital mortality in tricuspid valve surgery: A focus on the tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio

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ABSTRACT

Objectives: This study aimed to investigate the association between the tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio and in-hospital mortality in patients undergoing tricuspid valve replacement or repair.

Patients and methods: A retrospective evaluation was conducted with 302 consecutive patients (182 females, 120 males; mean age: 59.5±11.7 years) who underwent surgical intervention on the tricuspid valve at our tertiary center between January 2019 and January 2022. The final endpoint of the study was determined as in-hospital mortality. Patients were divided into two groups: those who developed in-hospital mortality and those who did not. Regression analyses were conducted to identify the independent variables.

Results: Forty-eight patients died in the hospital. Multivariate logistic regression analysis aimed at determining the predictors of in-hospital mortality identified age (p=0.023), TAPSE/PASP (p=0.024), and hospital stay duration (p<0.001) as independent determinants of in-hospital mortality. A receiver operating characteristic curve was plotted, and a cutoff value of 0.30 was determined using the Youden index (area under the curve=0.692, 95% confidence interval 0.609-0.774, p<0.001). This cutoff value could detect in-hospital mortality with a sensitivity of 66.8% and specificity of 68.7%.

Conclusion: The TAPSE/PASP ratio, a simple echocardiographic score, is associated with in-hospital mortality in patients undergoing tricuspid valve replacement or repair.

Keywords: Mortality, TAPSE/PASP, tricuspid valve surgery.

Tricuspid valve (TV) disease, either organic or secondary to other cardiac conditions, namely mitral valve disease or atrial fibrillation, is relatively common. The incidence of tricuspid regurgitation is observed in 0.55% of the general population and 4% of patients aged above 75 years.[1] Although the main background of severe tricuspid disease is mostly mitral stenosis or regurgitation,[2] atrial fibrillation,[3] or an implanted cardiac device,[4] 8.1% of patients with TV regurgitation do not have other valve diseases.[5] Surgery is indicated in symptomatic patients with severe tricuspid regurgitation and stenosis, irrespective of the cause.[2]

Surgical treatment of TV disease, either TV replacement or repair, has an increased mortality rate.[6] Several studies have shown the superiority of TV repair to TV replacement. Patients with valve replacement have increased all caused mortality rates and increased in-hospital stay.[7,8] Right ventricular mid-cavity length and TV tenting area were shown to be long-term predictors of one-year mortality after TV annuloplasty.[9] Regarding the short-term prognosis of TV surgery, TRI-SCORE, which is based on clinical and laboratory variables, was shown to be a predictor of in-hospital mortality.[10] Sarcopenia was demonstrated as an independent risk factor of increased in-hospital stay in this patient group.[11]

The tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio is a simple echocardiographic score and is found to be related to increased mortality in various

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diseases. Initially, it was reported that a lower TAPSE/PASP ratio is related to increased mortality in patients with pulmonary embolism.[12] Recently, this ratio was found to be a beneficial marker of mortality in patients with cardiac amyloidosis.[13] A lower TAPSE/PASP ratio was represented as a marker of development of pulmonary arterial hypertension.[14] This study aimed to investigate the relationship between in-hospital stay and the TAPSE/PASP ratio in patients who underwent TV replacement or repair.

PATIENTS AND METHODS

This retrospective study included 450 consecutive symptomatic patients with severe TV disease who underwent TV surgery at the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiology between January 2019 and January 2022. Patients with severe and symptomatic TV disease were discussed by the heart team, and surgical decisions were made by this team. Exclusion criteria were as follows: patients with systemic inflammatory diseases, those with chronic autoimmune disease, patients with active systemic infections, urgent operation due to any cause, and patients with a prior history of type 1-3 pulmonary arterial hypertension. After exclusion criteria were applied, 302 patients (182 females, 120 males; mean age: 59.5±11.7 years) were enrolled in this study.

The demographic information, clinical features, laboratory values, and echocardiography variables were obtained from patient files and hospital records. Routine blood tests were performed to assess complete blood count, lipid profile, complete blood count, serum C-reactive protein, and albumin levels. Blood samples were obtained from a forearm vein after a 12-h fast before performing the endovascular intervention. A Cobas 8000 c502 (Roche Holding AG, Basel, Switzerland) analyzer was used to evaluate serum C-reactive protein and albumin levels. Hospital stay time and the duration of mechanical intubation requirement were recorded. For each patient, the EuroSCORE II was calculated (https://www.euroscore.org).

Preprocedural transthoracic echocardiography was performed in each participant. An experienced echocardiographer performed all the echocardiographic evaluations using an echocardiography device with a 3.2-mHz adult probe (GE Vingmed Ultrasound AS, Horten, Norway).

Tricuspid annular plane systolic excursion is a parameter of longitudinal systolic performance of the right ventricle. Apical four-chamber view was used to obtain TAPSE values.[15] The M-mode precursor was aligned along the right ventricular free wall perpendicular to the lateral tricuspid annulus. The distance moved by the leading edge of the annulus from end-diastole toward the apex at end-systole was measured.[16]

Maximum tricuspid regurgitation was obtained either in four-chamber view or a right ventricle-focused four-chamber view. The Bernoulli equation was used to calculate the systolic pulmonary artery pressure.[16]

Statistical analysis

Data were analyzed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). To assess the normal distribution of variables, visual methods such as histograms and probability plots were employed alongside the Kolmogorov-Smirnov test. Numerical variables with a normal distribution were presented as mean ± standard deviation (SD), while numerical variables without a normal distribution were presented as median (interquartile range). Categorical variables were expressed as frequency (%). To determine the predictive value of the TAPSE/PASP value for the development of in-hospital mortality, receiver operating characteristic (ROC) curve and the Youden index [max (sensitivity + specificity -1)] were used. Numerical variables were compared between the two groups using the unpaired Student's t-test and the Mann-Whitney U test, depending on the distribution. Categorical variables were compared using the chi-square test or Fisher exact test. Univariate and multivariate logistic regression analyses were performed to determine the independent determinants of in-hospital mortality. The level of statistical significance was set at $p<0.05$, and an area under the ROC curve (AUC) >0.5 was considered statistically significant.

RESULTS

During the follow-up period, 48 patients died in the hospital. Patients were divided into two groups: patients with in-hospital mortality (non-survivors) and patients without in-hospital mortality (survivors). The baseline demographic, laboratory, and procedural data of the study group are presented

Table 1
Demographic, clinical, and procedural characteristics of the study group

	All patient (n=302)					Survivor group (n=254)					Non-survivor group (n=48)					
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)			59.5±11.7					58.5±11.9					64.6±8.6			**0.001**
Sex																
Female	182	60.3				155	61				27	56.3				0.535
Body surface area (cm^2)			1.8±0.18					1.81±0.18					1.79±0.16			0.440
Diabetes mellitus	108	35.8				85	33.5				23	47.9				0.055
Hypertension	158	52.3				136	53.5				22	45.8				0.327
COPD	56	18.5				44	17.3				12	25				0.209
Coronary artery disease	120	39.7				103	40.6				17	35.4				0.505
Smoking	35	11.6				25	9.8				10	20.8				**0.029**
Atrial fibrillation	222	73.5				191	75.2				31	64.6				0.126
Pacemaker	15	5				10	3.9				5	10.4				0.058
Congestive heart failure	69	22.8				53	20.9				16	33.3				0.059
Pulmonary hypertension	273	91				227	90.1				46	95.8				0.202
Albumin (g/dL)			3.98±0.62					4±0.6					3.9±0.6			0.506
Creatinine (mg/dL)				0.89	0.71-1.1				0.89	0.72-1.08				0.91	0.68-1.14	0.689
Leukocyte (10^3/uL)			7.76±2.36					7.8±2.3					7.7±2.6			0.910
Hemoglobin (g/dL)			12.5±2.1					12.5±2					12.3±2.4			0.577
Alanine transaminase (U/L)				16	12-24				16	12-23				19	12.3-28.5	0.135
Platelets (10^3/uL)				238	186-294.5				243	189-299.5				219	174.8-265	0.082
Hemoglobin A1c (%)			6.3±0.87					6.3±0.86					6.3±0.93			0.931
LVEF (%)			53.4±9					53.8±9					51±9.1			**0.044**
RVs			10.5±1.6					10.6±1.7					9.8±1.4			**0.004**
TAPSE			17.3±3.7					17.7±3.6					15.5±3.5			**<0.001**
PASP			51.8±14.9					50.8±14.5					57.1±15.8			**0.007**
TAPSE/ PASP			0.37±0.15					0.38±0.16					0.30±0.12			**<0.001**
Mitral valve replacement	281	93				238	93.7				43	89.6				0.304
Aortic valve replacement	79	26.2				61	24				18	37.5				0.051
CABG	56	18.5				45	17.7				11	37.5				0.395
Tricuspid surgery																0.612
Tricuspid valve replacement	104	34.4				89	85.6				15	14.4				
Tricuspid valve plasty	198	65.6				165	83.3				33	16.7				
Left atrium ligation	33	10.9				29	11.4				4	8.3				0.530
Ablation	8	2.6				8	3.1				0	0				0.213
Cardiopulmonary bypass time				126	105-154				122	103.5-154				137	115.3-159.8	0.056
Cross clamp time			89.9±33.3					88.8±32					96.2±39.8			0.163
Hospital stay (days)				11.5	8-17				11	8-16				18	9-41	**<0.001**
ICU stay (days)				3	2-6				3	2-5.3				12	4-26.8	**<0.001**
Intubation duration (days)				1	1-2				1	1-2				2	1-9	**<0.001**
EuroSCORE II			2.72±2.1							2.40±1.88			4.22±2.88			0.056

IQR: Interquartile range; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricular ejection fraction; RVs: Right ventricle free wall tissue doppler systolic wave; TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary arterial systolic pressure; CABG: Coronary artery bypass graft; ICU: Intensive care unit.

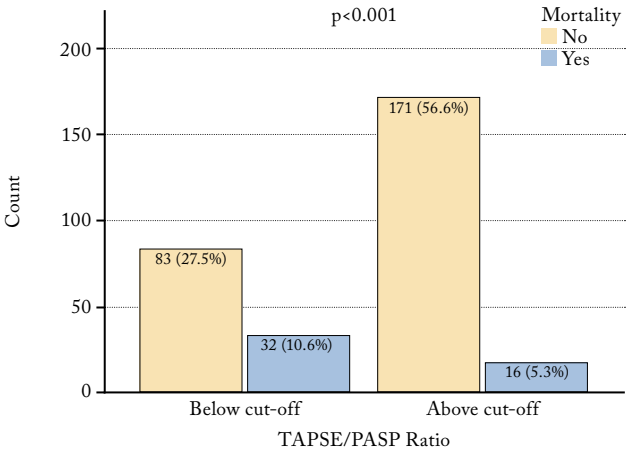

Figure 1. Distribution of TAPSE/PASP cutoff values among groups with in-hospital mortality.

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary arterial systolic pressure.

in Table 1. The two groups were comparable in terms of demographic characteristics, except for age (p=0.001) and smoking (p=0.029). These parameters were higher in the nonsurvivors group. No significant differences were found between the two groups in terms of laboratory parameters. Regarding echocardiographic parameters, PASP (p=0.007) was higher in the nonsurvivors group, whereas in the survivors group, LVEF (53.8±9% *vs.* 51±9.1%, p=0.044), tissue Doppler imaging of right ventricular free walls (10.6±1.7 *vs.* 9.8±1.4, p=0.004), TAPSE (17.7±3.6 *vs.* 15.5±3.5, p<0.001), and TAPSE/PASP (0.38±0.16 *vs.* 0.30±0.12, p<0.001) were higher compared to the nonsurvivors group. In terms of postoperative follow-up, hospital stay (18 [9-41] *vs.* 11 [8-16], p<0.001), the duration of intensive care unit stay (18 [9-41] *vs.* 11 [8-16], p<0.001), and intubation duration (12 [4-26.8] *vs.* 3 [2-5.3], p<0.001) were significantly higher in the nonsurvivors group compared to the survivors. Figure 1 illustrates the relationship between patients' TAPSE/PASP value and in-hospital mortality. According to these results, two-thirds of patients who experienced mortality had a TAPSE/PASP value below the cutoff point.

In Table 2, the surgical procedures performed on the patients were as follows: six (2%) patients underwent TV replacement and coronary artery bypass grafting, 46 (15.2%) patients underwent double valve replacement and coronary artery bypass grafting, 62 (20.5%) patients underwent triple valve replacement, 182 (60.3%) patients underwent double valve replacement, and six (2%) patients underwent isolated TV replacement or repair. There was no clear association between surgery subtypes and in-hospital mortality.

Univariate logistic regression analyses were conducted with all parameters to determine the predictors of in-hospital mortality in patients. Among the parameters significantly associated with in-hospital mortality, age, smoking, LVEF, tissue Doppler imaging of right ventricular free walls, TAPSE/PASP, and duration of in-hospital stay are presented in Table 3. In the multivariate logistic regression analysis conducted using these variables, age (p=0.023), TAPSE/PASP (p=0.024), and hospital stay duration (p<0.001) emerged as

Table 2
Distribution of operation types

	All patient (n=302)		Survivor group (n=254)		Non-survivor group (n=48)		
Surgery type	n	%	n	%	n	%	*p*
Isolated tricuspid valve surgery	6	2	5	2	1	2.1	
Combined mitral and tricuspid valve surgery	172	57	152	59.8	20	41.7	
Combined aortic and tricuspid valve surgery	10	3.3	7	2.8	3	6.3	
Combined aortic, mitral and tricuspid valve surgery	62	20.5	49	19.3	13	27.1	0.230
Combined mitral and tricuspid valve and CABG surgery	42	13.9	33	13	9	18.8	
Combined aortic and tricuspid valve and CABG surgery	4	1.3	4	1.6	0	0	
Combined aortic, mitral and tricuspid valve and CABG surgery	6	2	4	1.6	2	4.2	

CABG: Coronary artery bypass graft.

Table 3
Independent predictors for in-hospital mortality with univariate and multivariate logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.057	1.023-1.093	**0.001**	1.046	1.006-1.087	**0.023**
Smoking	2.411	1.073-5.417	**0.033**	2.215	0.843-5.819	0.107
LVEF	0.968	0.938-0.999	**0.046**	0.985	0.757-1.282	0.910
RVS	0.754	0.620-0.916	**0.004**	0.955	0.751-1.215	0.708
TAPSE/PASP	0.281	0.148-0.533	**0.001**	0.369	0.155-0.876	**0.024**
Hospital stay	1.056	1.034-1.079	**<0.001**	1.045	1.022-1.069	**<0.001**

OR: Odds ratio; CI: Confidence interval; LVEF: Left ventricular ejection fraction; RSV: Systolic annular tissue velocity of the lateral tricuspid annulus; TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary arterial systolic pressure.

independent determinants of in-hospital mortality. A ROC curve was plotted to determine the optimal cut-off value for TAPSE/PASP that best detects in-hospital mortality (Figure 2), and a cutoff value of 0.30 was determined using the Youden index (AUC=0.692, 95% confidence interval 0.609-0.774, p<0.001). This cutoff value could detect in-hospital mortality with a sensitivity of 66.8% and specificity of 68.7%.

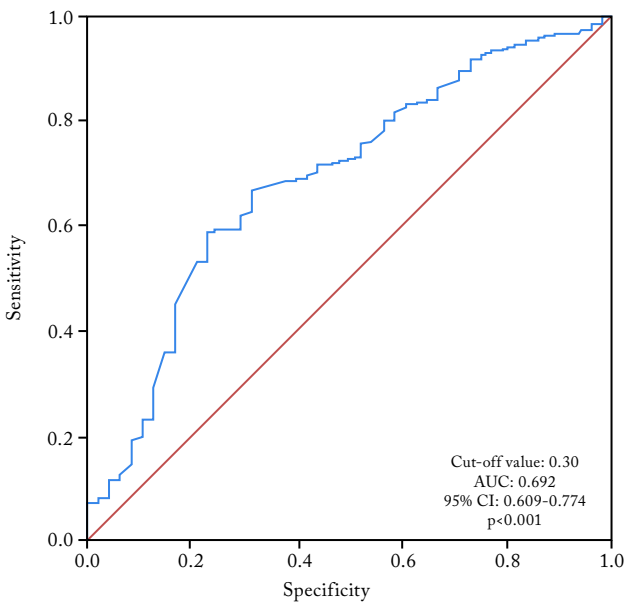

Figure 2. The ROC curve for TAPSE/PASP as a predictor of in-hospital mortality.

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary arterial systolic pressure.

DISCUSSION

Through this study, we investigated the relationship between the TAPSE/PASP ratio and in-hospital mortality of surgically treated TV disease. Noteworthy this research highlights:

- TAPSE/PASP ratio is an independent predictor of in-hospital mortality in patients, who underwent TV surgery.

- Advanced age is an independent rick factor of in-hospital mortality in such patient group. With regard to the current knowledge, this present study is the first data, which represents the relationship with lower TAPSE/PASP ratio and in-hospital mortality in this patient group in literature.

Open repair or replacement of the TV is a high-risk operation. Kawsara et al.[6] have recently represented that 8.7% of surgically treated patients have in-hospital mortality. In the same data, acute heart failure signs and symptoms, nonelective surgery, and liver dysfunction were shown to be the independent predictors of in-hospital mortality. However, this study was performed in patients with isolated TV disease. The majority of our patients underwent surgery due to concomitant valve diseases or coronary artery.

With regard to long-term mortality, Wong et al.[7] illustrated that only 12.6% of patients underwent isolated TV surgery among 2,644 patients. In this data, it is clearly shown that TV replacement is an independent predictor of all-cause long-term mortality. With respect to our findings, there is no

clear difference between TV replacement and repair in term of in-hospital mortality. Long-term findings are required in our patient group.

The TRI-SCORE is a relatively new score, which is shown to be an independent predictor of in-hospital mortality in patients who underwent surgery due to isolated TV disease. This score consists of clinical, echocardiographic, and laboratory parameters, namely advanced age, clinical status evaluated by the New York Heart Association system, right-sided heart failure signs and symptoms, requirement of high-dose loop diuretics, deterioration of renal status, elevated total bilirubin, worsening of ejection fraction, and moderate to severe right ventricular systolic function.[10] Dreyfus et al.[10] showed that an advanced TRI-SCORE predicts not only in-hospital but also one-year mortality in 466 patients who were surgically treated due to isolated TV disease. Similarly, advanced age is also an independent risk factor for our patients. The main difference of our study is that the vast majority of our patients were operated on due to concomitant valve and coronary diseases. Yiu et al.[9] illustrated that right ventricular mid-cavitary dimensions and increased TV tenting area predict one-year mortality in 74 patients who underwent TV surgery due to concomitant valve disease. According to this study, the right ventricle diameter and tenting area should be measured before concomitant valve surgeries.

The TAPSE/PASP ratio is a simple scoring system based on the echocardiograhic calculations of TAPSE and PASP. This scoring system has been shown to be beneficial in various patient groups. Çolak et al.[12] demonstrated that a TAPSE/PASP ratio <0.20, combined with worse clinical status, is related to poor prognosis in patients with chronic thromboembolic pulmonary hypertension.

In a study with a median follow-up period of 680 days, Maccallini et al.[13] illustrated that an increased TAPSE/PASP ratio is associated with increased long-term survival and hospitalization-free survival rates in 233 patients with cardiac amyloidosis. Moreover, among 2,555 patients with systemic sclerosis, a TAPSE/PASP ratio <0.55 was an independent risk factor of development for the pulmonary arterial hypertension.[14] The TAPSE/PASP could be considered a risk factor of all-cause mortality.[14]

In our data, we aimed to identify the risk factors of in-hospital mortality in this patient group. Similar to previous studies, advanced age was shown to be the independent predictor of in-hospital mortality.[15,16] This simple, cost-effective, and time-saving method was shown to be functional in predicting short-term prognosis in patients who underwent TV surgery. To the best of our knowledge, this is the first study that represents such a relationship.

There are several limitations to this study. First, it was a retrospective study conducted with a relatively limited number of patients. Second, this study was performed in a heterogeneous patient group. The vast majority of studies have been performed in patients who have been operated on due to isolated TV disease. Third, long-term findings of the patients were required. Finally, there is no clear cutoff value of the TAPSE/PASP ratio in various patient groups. Further studies are needed to identify this value.

In conclusion, a decreased TAPSE/PASP ratio is related to a deterioration in short-term outcomes and in-hospital mortality in patients who underwent TV surgery. It is a valid and time-saving scoring system that can be used daily in clinical practice. The scoring system can be used to identify high-risk patients, allowing for more meticulous preoperative and postoperative evaluations, thereby reducing mortality rates.

Ethics Committee Approval: The study protocol was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee (date: 27.02.2024, no: 2024.01.13). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study design, statistics, overwiew: A.A.; Writing and references: T.A.

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Cardiovascular Surgery and Interventions

Original Article Open Access

Analysis of incorrect referrals to the cardiovascular surgery outpatient clinic

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ABSTRACT

Objectives: This study aimed to determine the rate of incorrect referrals to the cardiovascular surgery outpatient clinic.

Patients and methods: This study retrospectively reviewed the electronic patient records of patients admitted to a cardiovascular surgery outpatient clinic between July 1, 2021, and December 1, 2022. Patients were categorized into the incorrect referral group and the appropriate admission group. Patients who should have initially presented to the cardiology outpatient clinic for symptoms such as palpitations, exertional chest pain, echocardiography control, and routine cardiac check-ups were classified as incorrect referrals. Age, sex, and Central Physician Appointment System usage were the other variables recorded in the study.

Results: Of the 2,675 patients (1,540 females, 1,135 males; mean age: 53.3±18.0 years; range, 5 to 97 years) evaluated in the study, 316 (11.8%) were categorized into the incorrect referral group. The rate of incorrect referral was 18.63% for patients who applied through the Central Physician Appointment System, whereas it was 4.43% for those who applied without an appointment. There was a significant relationship between the Central Physician Appointment System use and incorrect referral ($p<0.001$). Multivariate logistic regression model showed that both age and the use of the Central Physician Appointment System independently predicted inappropriate visits ($p<0.001$).

Conclusion: The Central Physician Appointment System alone is inadequate to prevent inappropriate admissions. Enhancing the role of artificial intelligence in the appointment system, improving health literacy, and simplifying branch names are potential changes that can be implemented to prevent incorrect referrals.

Keywords: Cardiology, cardiovascular surgery, central physician appointment system, outpatient clinic, referral and consultation.

Outpatient clinic examinations constitute an important branch of healthcare services. It is crucial for patients to apply to the appropriate outpatient clinics based on their complaints and receive healthcare promptly. Over the years, the growing population, challenges in implementing the healthcare level system, and a shortage of physicians have collectively resulted in an increased density of outpatient clinics. The Central Physician Appointment System (CPAS) was introduced by the Ministry of Health in 2010 as part of the Health Transformation Project. The primary objectives were to reduce waiting times before examinations, reduce in-hospital crowding, direct patients to the appropriate outpatient clinics based on their complaints, and prevent the loss of physician workforce.[1]

The CPAS can be accessed through various channels, including the support of the "182" call center, internet, and mobile application. Additionally, it is available through hospitals and family physicians. The primary objective of the artificial intelligence-based "What is wrong with me?" application and operator system of CPAS is to generate appropriate appointments for patients who report their complaints, ensuring that they are directed to the right medical branch.[2]

In Türkiye, the number of hospital admissions via appointments for 2022 was approximately

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110 million.[3] However, the total number of examinations is significantly higher than this figure for the same year as indicated by the Health Services Utilization Statistics report.[4] Despite its introduction to reduce overcrowding in outpatient clinics, the CPAS system has not fully met expectations in addressing appointment requests. Therefore, in addition to CPAS applications, outpatient clinic services are also provided to patients without appointments. In a single-center study assessing the effectiveness of the CPAS, the majority of outpatient clinic visits were reported to be conducted without an appointment.[5]

Considering the rising number of outpatient clinic admissions and the growing workload of healthcare professionals, it is crucial to accurately guide patients to the appropriate outpatient clinics. The objective of the current study is to determine the rate of patients presenting to the cardiovascular surgery outpatient clinic who should have been referred to the cardiology outpatient clinic and assess the potential reasons for such instances.

Diagnostic tools such as echocardiography, rhythm Holter, and coronary angiography are within the domain of the cardiology department, utilized in the process of diagnosing cardiac symptoms and ultimately leading to surgical decisions. Therefore, initial referrals to the cardiovascular surgery outpatient clinic based on these symptoms have been termed incorrect referrals.[6-8] This study aimed to determine the rate of incorrect referrals to the cardiovascular surgery outpatient clinic.

PATIENTS AND METHODS

Patients admitted to the cardiovascular surgery outpatient clinic at the Burdur State Hospital between July 1, 2021, and December 1, 2022, were retrospectively analyzed. Patients who were admitted to the cardiovascular surgery outpatient clinic before the study date were excluded. For patients with multiple admissions after July 1, 2021, only the initial application was considered. The admission records were then electronically reviewed and categorized into two groups: the incorrect referral group and the correct referral group. Incorrect referral was defined as patients who should have initially presented to the cardiology outpatient clinic for symptoms such as palpitations and exertional chest pain, echocardiography follow-up, and routine cardiology check-ups. Age, sex, and CPAS usage were the other variables recorded in the study.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA) software. The Kolmogorov-Smirnov test was employed to assess the fitness of variables to a normal distribution. Due to the nonnormal distribution, the data were analyzed using nonparametric tests. When post hoc power analysis was conducted based on the attained sample size, the power was calculated as 88%, with an effect size (d) of 0.2 and an alpha (α) of 0.05. The data were analyzed using descriptive statistics (number, percentage, median, and interquartile range), the Mann-Whitney U test, chi-square test, and logistic regression analysis. The significance level was set at $p<0.05$.

RESULTS

Among the 2,675 patients (1,540 females, 1,135 males; mean age: 53.3±18.0 years; range, 5 to 97 years) meeting the inclusion criteria, 316 (11.8%) were classified in the incorrect referral group, while 2,359 (88.18%) were categorized in the correct referral group. Of the patients, 42.43% were male, and 57.57% were female. The median age in the incorrect referral group was 41 years, whereas it was 56 years in the correct referral group. There was statistically

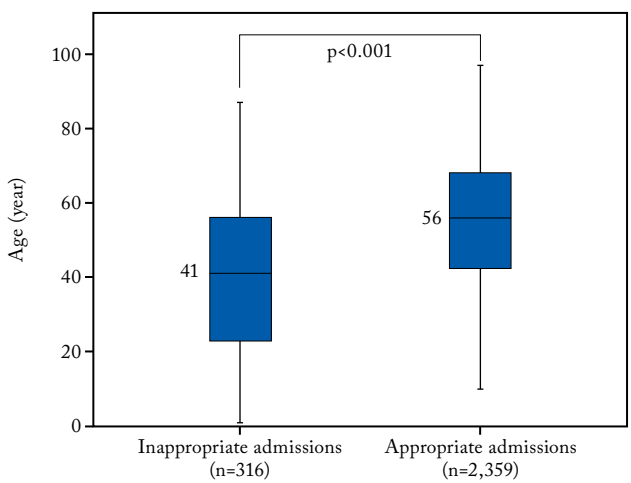

Figure 1. Age of patients in the incorrect and correct referral groups.

Table 1
Patient characteristics and distribution by groups

	Incorrect referral application (n=316)				Correct referral (n=2,359)				
	n	%	Median	IQR	n	%	Median	IQR	*p*
Age			41	33			56	26	<0.001*
Sex									0.295**
Male	139	12.25			996	87.75			
Female	177	11.5			1,363	88.5			
CPAS usage									<0.001**
Yes	259	18.63			1,131	81.37			
No	57	4.43			1,228	95.57			

IQR: Interquartile range; CPAS: Central Physician Appointment System; * Mann-Whitney U test; ** Chi-square test.

Table 2
Evaluation of the role of variables in predicting incorrect referrals using logistic regression

	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	0.958	0.951-0.965	<0.001	0.961	0.954-0.968	<0.001
Sex	1.075	0.848-1.362	0.551			
CPAS usage	4.93	3.663-6.646	<0.001	4.34	3.209-5.886	<0.001

OR: Odds ratio; CI: Confidence interval; CPAS: Central Physician Appointment System.

significant difference between the two groups in terms of age (p<0.001, Figure 1).

The variables pertaining to the incorrect referral and correct referral groups are presented in Table 1. The rate of incorrect referrals was 12.25% among the male patients and 11.5% among the female patients. There was no statistically significant relationship between sex and incorrect referrals (p=0.295). The rate of incorrect referrals was 18.63% among patients who used the CPAS, whereas the rate was 4.43% in outpatient clinic visits without an appointment. There was a significant relationship between the use of the CPAS and the incidence of incorrect referrals (p<0.001).

The role of variables in predicting incorrect referrals was evaluated through univariate and multivariate logistic regression analyses. Univariate logistic regression analysis revealed that younger age and CPAS use significantly predicted incorrect referrals (p<0.001). Multivariate logistic regression model using age (odds ratio [OR]=0.961, 95% confidence interval [CI]: 0.954-0.968, p<0.001) and CPAS use (OR=4.34, 95% CI: 3.209-5.886, p<0.001) showed that both age and CPAS use independently predicted incorrect referrals (p<0.001, Table 2).

DISCUSSION

Early diagnosis, regular follow-up of chronic diseases, informing patients, and providing preventive medicine services are among the primary objectives of outpatient clinic examinations. According to the Health Services Utilization Statistics report, the number of applications to hospitals affiliated with the Ministry of Health for 2022 was approximately 375 million.[4] Due to the disproportionate increase in the number of applications, patients are facing challenges in accessing healthcare services. Patients can receive appropriate healthcare services only if they can promptly apply to the right outpatient clinic. The CPAS developed by the Ministry of Health has been employed for this purpose since 2010. Despite its advantages, such as ease of use and the provision of services via mobile phones, call centers, and websites, the CPAS is inadequate in preventing incorrect referrals to outpatient clinics.

This is the first study to examine incorrect referrals to the cardiovascular surgery outpatient clinic. In our study, the rate of incorrect referrals to the cardiovascular surgery outpatient clinic was 11.5%. According to the Ministry of Health data, the reported rate of referral to an incorrect department was 6%.[2] In a study evaluating referrals to the internal medicine outpatient clinic, the reported rate of incorrect referrals was 3%.[9] Zorlu and Kavurmacı[10] evaluated the rate of incorrect referrals among patients who presented to the thoracic surgery outpatient clinic via CPAS. In their study, the rate of patients who were referred to the thoracic surgery outpatient clinic when they should have been directed to the thoracic diseases outpatient clinic was approximately 6%. The rate of incorrect referrals found in the present study is significantly higher than the rates reported in the previous studies.

The incidence of one in 10 patient visits to the cardiovascular surgery outpatient clinic as an incorrect referral has several potential consequences: *(i)* delay in diagnosis and treatment of the patient; *(ii)* communication issue between the patient and physician; *(iii)* loss of labor force; *(iv)* patients who present to the correct department may not have the opportunity to be examined.

In a study conducted by Solmaz and Uluda,[11] admissions to the cardiology outpatient clinic were analyzed, and the rates of admissions with noncardiac complaints were evaluated. The rate of admission with noncardiac complaints was significantly higher in the CPAS group than in the no-appointment group. Similarly, in our study, the rate of CPAS use was significantly higher in the incorrect referral group, and CPAS use was associated with a 4.34-fold increase in incorrect referrals. This situation contradicts the principles of time management and the appropriate referral to the right branch, which are the main objectives of CPAS. The high rate of correct referrals among patients presenting without an appointment can be explained by the effective functioning of in-hospital referral mechanisms. Some factors that may explain the high rate of incorrect referrals among patients who made appointments through CPAS are as follows. First, inadequate knowledge and low health literacy level of the patient may explain the appointment to the wrong branch. The second factor is the confusion in branch names. The term "cardiovascular surgery" is simpler and more understandable than "cardiology" when selecting a specialty. Third is the misdirection caused by the CPAS. Patients who use CPAS by contacting the 182 hotline officials or the "What is wrong with me?" application may be directed to the cardiovascular surgery branch instead of cardiology.

Another finding of the study is the relationship between young age and incorrect referrals. Young age was associated with incorrect referrals independent of CPAS use. This could be explained by the likelihood that patients in the older age group are more health-conscious or have higher exposure to the healthcare system.

Steps for improvement identified based on the findings may contribute to the reduction of incorrect referrals to the cardiovascular surgery outpatient clinic. Some changes can be made in this direction. Professional associations should provide the public with accurate and understandable information about cardiovascular surgery and be active on social media platforms. The confusion in branch names should be eliminated. Furthermore, assessing the knowledge level of the 182 hotline employees and collaborating with professional associations to provide branch-specific information could lead to improvement. Finally, the artificial intelligence-supported "What is wrong with me?" application should be updated and developed to be consistent with developments in the field of health professionals and artificial intelligence.

Another intervention that can be implemented to prevent incorrect referrals, both for patients with appointments through CPAS and those without appointments, is the effective use of the healthcare level system. According to data from the Ministry of Health, only 40% of the over 850 million presentations made in 2022 were primary care admissions.[4] This reveals that direct admissions to secondary and tertiary care are predominant. Directing patients to the right specialty and appropriate health center is among the primary objectives of family medicine practice.[12] While there may be certain differences in each healthcare level, the primary purpose of family medicine often revolves around the referral chain. Numerous studies have demonstrated that the implementation of a referral chain decreases the number of outpatient clinic visits.[13-15] The implementation of the referral chain is vital in preventing both unnecessary and incorrect admissions. According to Bektemur et al.,[16] 85% of physicians in the family

medicine system stated that referral chain should be implemented, while only 55% believed that referral chain was feasible in Türkiye. We believe that improvements in the family medicine system and modifications to the referral chain system in Türkiye will be effective in preventing incorrect referrals.

This study has some limitations. The study was conducted in a single center. Multicenter studies examining incorrect outpatient clinic referrals may contribute to the overall understanding of the results. In the study, incorrect referral was defined as patients who should have initially presented to the cardiology outpatient clinic, which represents the second limitation of the study. The evaluation of all incorrect referrals to the cardiovascular surgery outpatient clinic may result in a rate that is significantly higher than the rate found in this study. The last limitation of the study is that it was conducted retrospectively. Surveys investigating the reasons why patients incorrectly present to the cardiovascular surgery outpatient clinic may contribute to revealing the existing problems with the appointment system.

In conclusion, healthcare workers are serving beyond their capacity due to the increasing number of patient admissions every day. This situation negatively affects both patients receiving services and healthcare professionals. The increasing demand for appointments over the years has resulted in a reduction in examination times. Although CPAS, developed by the Ministry of Health, is continuously improving in terms of preventing time wastage and providing accurate guidance with technological advancements, it alone is inadequate to prevent incorrect referrals. Developing systems to prevent incorrect referrals will ensure that the correct patients requiring services have access to healthcare earlier and protect health workers from unnecessary workload.

Ethics Committee Approval: The study protocol was approved by the Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (date: 12.01.2023 no: 1.6). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, data collection and/or procesing: Ö.F.R.; Control/supervision, analysis and/or interpretation, literature review, writing the article, critical review, references, materials: Ö.F.R., F.A.

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Link between lower extremity venous reflux and varicocele in adult male patients: A prospective study

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ABSTRACT

Objectives: This study aimed to investigate the relationship between lower extremity venous reflux and varicocele in adult males.

Patients and methods: A total of 102 adult male patients (mean age: 42.7±15.5 years; range, 20 to 82 years) with complaints of burning, cramps, swelling with prolonged standing, and superficial varicose veins were enrolled in the prospective study between January 2023 and June 2023. All patients were subjected to bilateral lower extremity venous and scrotal Doppler ultrasonography.

Results: Varicocele was more frequently observed in individuals with left vena saphena magna (VSM) reflux compared to those without (p=0.001). Similarly, varicocele was more prevalent in individuals with left VSM insufficiency compared to those without (p=0.008). However, there was no significant relationship between right VSM insufficiency, right VSM reflux, and pampiniform reflux on either side (p>0.05).

Conclusion: In patients with reflux in the left VSM, pampiniform reflux and varicocele are more frequently observed. This finding can provide valuable clues for the early diagnosis of varicocele, particularly for urologists, vascular surgeons, and radiologists.

Keywords: Doppler ultrasound, varicocele, venous reflux.

Chronic venous insufficiency is a commonly encountered vascular disorder in the community. Advancing age, obesity, pregnancies, prolonged periods of standing, positive family history, and Caucasian ethnicity are predisposing factors for chronic venous insufficiency.[1] Previous studies have proposed that chronic venous insufficiency shares similar pathogenesis with varicocele in males, emphasizing venous valve insufficiency, associated reflux, venous wall pathology, and May-Thurner syndrome as frequently suggested pathologies.[2-5]

Varicocele, observed in approximately 15% of the adult male population, has been identified as a major cause of infertility, affecting nearly 40% due to a decrease in sperm count and motility.[6] Diagnosis involves the palpation of dilated veins during physical examination or the demonstration of enlarged pampiniform veins through Doppler ultrasonography (USG), both playing a significant role.

This study aimed to investigate the potential connection between lower extremity venous reflux and varicocele in adult males.

PATIENTS AND METHODS

A total of 102 adult male patients (mean age: 42.7±15.5 years; range, 20 to 82 years) presenting with burning, cramps, swelling with prolonged standing, and superficial varicose veins at the cardiovascular surgery outpatient clinic of the Ağrı Training and Research Hospital between January 2023 and June 2023

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were enrolled in the prospective study. Patients with a history of venous thrombosis were excluded from the study (Figure 1).

After obtaining a medical history and conducting a physical examination, all patients were subjected to bilateral lower extremity venous and scrotal Doppler USG. A single radiologist performed measurements using a Toshiba Aplio 500 Ultrasound device (Canon Medical Systems USA, Inc., Tustin, CA, USA) during the same session (Figure 2). Measurements included diameter and reflux measurements of the vena saphena magna (VSM) at the junction level, as well as diameter and reflux measurements of bilateral pampiniform veins. The VSM reflux and pampiniform reflux were measured with the Valsalva maneuver. Standing measurements were taken for all patients. Reflux lasting more than 1 sec at the VSM junction level was considered positive.[7] Reflux flow lasting more than 1 sec along the course of the VSM at the thigh level following caudal decompression was considered VSM venous insufficiency. In scrotal Doppler USG, patients with a diameter of 3 mm or more on either side and reflux lasting more than 2 sec in the pampiniform plexus vein were considered to have varicocele, according to the 2019 guidelines published by the European Society of Urogenital Radiology Scrotal and Penile Imaging Working Group.[8]

Statistical analyses

The data obtained from the study were analyzed using the IBM SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was performed to assess normal distribution suitability. Descriptive statistics, including numbers and percentages, means, and standard deviations, were provided. The Mann-Whitney U test was employed to evaluate the relationship between two groups for measurement data that did not follow a normal distribution. The chi-square test was utilized to assess the relationship between categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

The sociodemographic characteristics and medical histories of the patients are presented in Table 1. In terms of occupation, 37.3% were workers, 16.7% were farmers, and 12.7% were retirees. Among the patients, 57.8% smoked, and 2.0% consumed alcohol. Additionally, 2.9% had diabetes mellitus (DM), 11.8% had hypertension (HT), and 1.9% had benign prostatic hyperplasia (BPH).

None of the patients exhibited venous ulcers or infertility. Scrotal pain was reported in 13.7% of the patients. Additionally, among the patients, 34.3% presented with right VSM insufficiency, 30.4% with right VSM reflux, 46.1% with left VSM insufficiency, 42.2% with left VSM reflux, and 26.5% with pampiniform reflux. Varicocele was observed in 34.3% of the patients. The mean diameter of the right VSM was 5.2±2.2, the mean diameter of the left VSM was

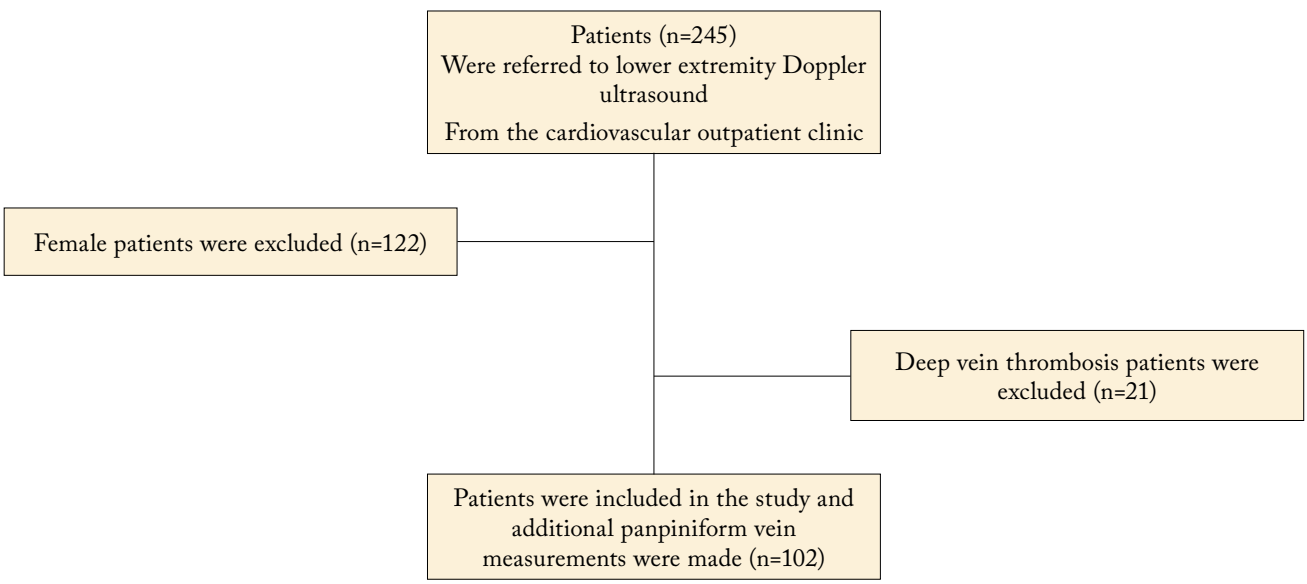

Figure 1. Flowchart of the study.

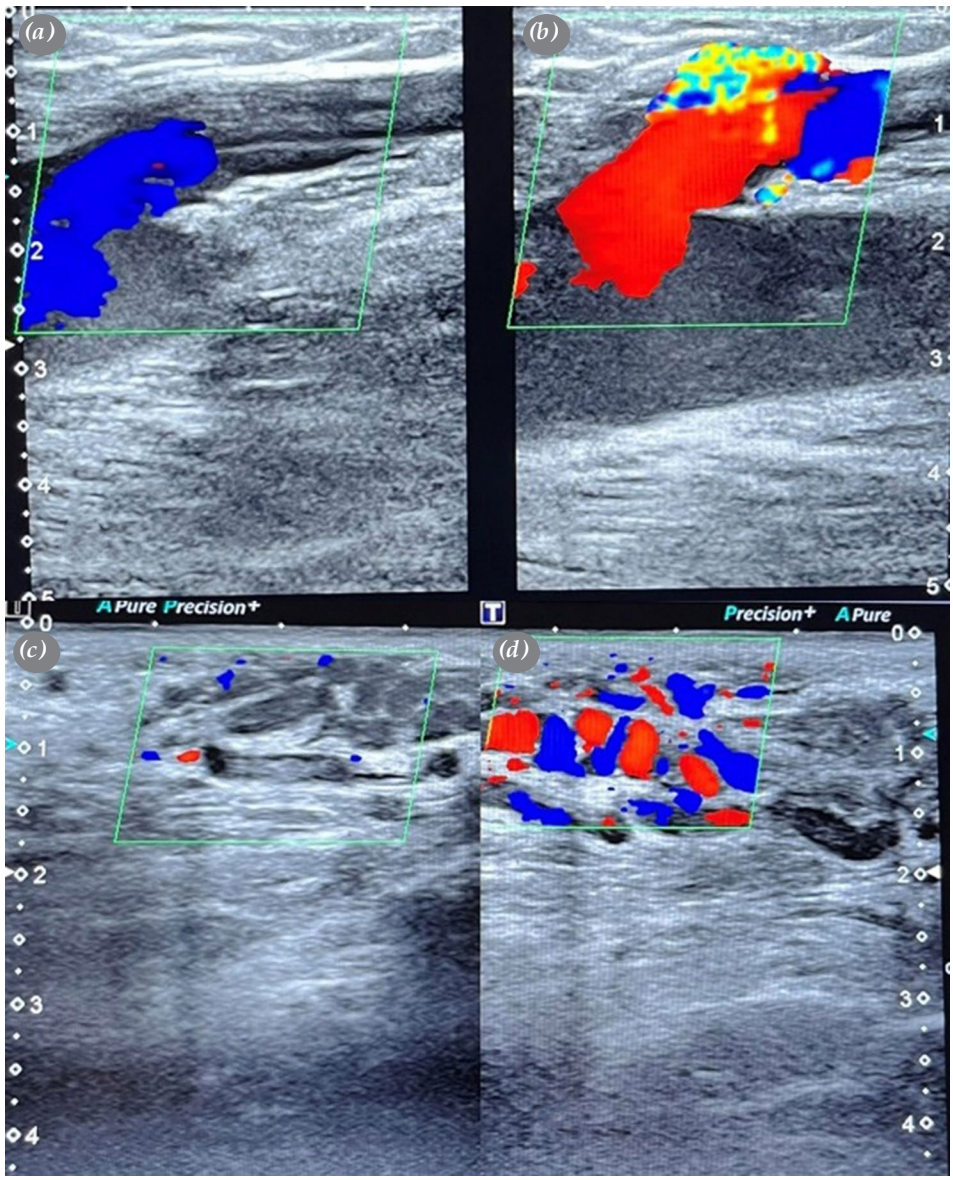

Figure 2. **(a)** Doppler USG of the same patient at the dilated VSM junctional level, **(b)** reflux at the VSM junctional level after the Valsalva maneuver, **(c)** dilated pampiniform veins, **(d)** reflux flow of the pampiniform veins after the Valsalva maneuver.
USG: Doppler ultrasonography; VSM: Vena saphena magna.

5.8±2.6, the maximum VSM diameter was 6.4±2.7, and the mean diameter of the pampiniform vein was 1.3±1.8 (Table 2).

Pampiniform reflux was more prevalent in those with left VSM reflux compared to those without (p=0.001). Similarly, individuals with left VSM insufficiency exhibited a higher occurrence of pampiniform reflux than those without (p=0.006). However, there was no significant relationship between right VSM insufficiency, right VSM reflux, and pampiniform reflux (p>0.05), as indicated in Table 3.

Varicocele was more frequently observed in individuals with left VSM reflux compared to those without (p=0.001). Similarly, varicocele was more prevalent in individuals with left VSM insufficiency compared to those without (p=0.008). However, there was no significant relationship between right VSM insufficiency, right VSM reflux, and

Table 1
Sociodemographic characteristics and medical histories of the patients

	n	%	Mean±SD
Age (year)			42.7±15.5
Job			
Laborer	38	37.3	
Officer	7	6.9	
Farmer	17	16.7	
Retire	13	12.7	
Soldier	9	8.8	
Police	4	3.9	
Security	4	3.9	
Health personnel	2	2.0	
Small business	4	3.9	
Other	4	3.9	
Smoker	59	57.8	
Diabetes mellitus	3	2.9	
Hypertension	12	11.8	
Benign prostatic hyperplasia	2	1.9	

SD: Standard deviation.

pampiniform reflux on either side (p>0.05), as outlined in Table 4.

No significant relationships were found between the presence of pampiniform reflux and age, alcohol use, diagnosis of DM, diagnosis of HT, and diagnosis of BPH (p>0.05). Pampiniform reflux was more frequently observed in nonsmokers compared to smokers (p=0.005). Additionally, pampiniform reflux was more prevalent in individuals with scrotal pain compared to those without (p<0.001).

Similarly, no significant relationships were detected between the presence of varicocele and age, alcohol use, and HT diagnosis (p>0.05). However, individuals diagnosed with BPH exhibited a higher prevalence of varicocele compared to those without (p=0.01). Varicocele was also more frequently observed in individuals with DM diagnosis compared to those without (p=0.04). Furthermore, individuals with scrotal pain had a higher prevalence of varicocele compared to those without (p<0.001).

Table 2
Clinical findings of the patients

	n	%	Mean±SD
Right VSM diameter (mm)			5.2±2.2
Left VSM diameter (mm)			5.8±2.6
Pampiniform vein diameter (mm)			1.3±1.8
Right VSM insufficiency	35	34.3	
Left VSM insufficiency	47	46.1	
Right VSM reflux	31	30.4	
Left VSM reflux	43	42.2	
Pampiniform vein reflux (right or left)	27	26.5	
Varicocele	35	34.3	
Scrotal pain	14	13.7	

SD: Standard deviation; VSM: Vena saphena magna.

Table 3
Relationships between pampiniform reflux, VSM reflux, and VSM insufficiency

	Pampiniform reflux (on any side)					
	Absent		Present			
	n	%	n	%	χ^2	*p*
Left VSM reflux	24	55.8	19	44.2	10.46	**0.001**
Right VSM reflux	22	71.0	9	29.0	0.02	0.89
Left VSM insufficiency	28	59.6	19	40.4	7.44	**0.006**
Right VSM insufficiency	26	74.3	9	25.7	0.0	1.00

VSM: Vena saphena magna.

Table 4
Relationships between varicocele and reflux and insufficiency

	Varicocele					
	Absent		Present			
	n	%	n	%	χ^2	p
Left VSM reflux	20	46.5	23	53.5	10.70	**0.001**
Right VSM reflux	20	64.5	11	35.5	0.00	1.00
Left VSM insufficiency	24	51.1	23	48.9	7.11	**0.008**
Right VSM insufficiency	24	68.6	11	31.4	0.05	0.82

VSM: Vena saphena magna.

DISCUSSION

In our study, left pampiniform reflux was found to be statistically significantly higher in patients with left VSM reflux. This could be attributed to anatomical reasons, such as the left testicular vein taking a 90° angle with the renal vein and the cross-adjacency of the left iliac vein and the right iliac artery.[9] Chin et al.,[10] in their research involving 21 varicocele patients, were the first to demonstrate that May-Thurner syndrome (compression of the left iliac vein) causes varicocele. Furthermore, a case report has demonstrated that May-Thurner syndrome could lead to varicocele by causing left internal iliac vein reflux.[11] Although our study suggests a significant association between varicocele and left venous reflux, the exact cause may be related to this condition. However, this study did not specifically investigate the presence of reflux in the internal iliac veins.

Another theory discussed in many previous studies regarding the relationship between venous reflux and varicocele is venous valve insufficiency as a shared etiology.[3,12,13] However, in our study, a statistically significant increase in varicocele was observed only in patients with venous reflux in the left VSM.

The relationship between varicocele and demographic data was investigated in our study, but no significant association was found. It is not surprising that varicocele is more prevalent in patients with scrotal pain complaints. In a study conducted by Owen et al.,[14] it was reported that scrotal pain accompanied varicocele in 10% of patients. On the other hand, none of the patients included in the study showed evidence of venous ulcers upon examination.

According to the report on varicocele and infertility published by the American Urological Association, even if patients diagnosed with varicocele do not complain of infertility, it is emphasized that sperm analysis should be performed. This is because patients may express a desire to have children in the future, and those with developed azoospermia should be treated.[15] Although none of the patients included in this study reported infertility complaints, all patients diagnosed with varicocele were referred to urology specialists for a thorough examination and sperm analysis, as they are considered potential candidates for secondary infertility. Additionally, patients with detected VSM reflux and dilation were treated with stripping, radiofrequency ablation, or medical follow-up (compression stockings and venoactive drugs).[16]

There are some limitations to this study. This study was planned with prospectively conducted Doppler measurements during the same session; however, sperm analysis and measurements of internal iliac vein reflux were not performed due to technical challenges. Additionally, the relatively low number of patients might limit the generalizability of the results, and conducting studies with larger sample sizes could yield more comprehensive outcomes.

In conclusion, in patients with reflux in the left VSM, pampiniform reflux and varicocele are more frequently observed on either side. This finding can provide a valuable clue for the early diagnosis of varicocele, particularly for urologists, vascular surgeons, and radiologists. Further extensive studies with a larger number of patients are needed in this regard.

Ethics Committee Approval: The study protocol was approved by the Ankara City Hospital Ethics Committee (date: 21.06.2023, no: 3577). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Cardiovascular Surgery and Interventions

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Investigation of effects of different drain materials on postoperative pleural complications and pain in off-pump surgery

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ABSTRACT

Objectives: This study aimed to investigate whether the need for thoracic tubes placed in the intercostal space, which cause severe pain in the postoperative period and significant problems in pulmonary rehabilitation, could be eliminated by Jackson-Pratt drains placed in the mediastinum in patients who undergo off-pump surgery.

Patients and methods: A prospective analysis of 129 patients (100 males, 29 females; mean age: 62.9±8.5 years; range, 44 to 82 years) who underwent routine off-pump isolated coronary artery bypass grafting surgery between January 2018 and December 2018 was performed. The number of patients who had subxiphoid mediastinal drainage and one mediastinal Jackson-Pratt drainage was 64 (Group 1), and the number of patients who had subxiphoid mediastinal drainage and intercostal chest drainage was 65 (Group 2). Postoperative pain scores, analgesic needs of patients, and radiological effusion and pneumothorax assessments were recorded, and pleural complications requiring invasive intervention were compared.

Results: There was no difference between the groups in terms of age, sex, and comorbidities. There was a significant superiority in Group 2 in terms of pain scoring in the first hour after extubation and the need for analgesia in all follow-up periods ($p<0.001$). In two (3.12%) patients in Group 1 and in two (3.07%) patients in Group 2, pleural effusion requiring intervention was detected. There was no significant difference between the two groups in terms of effusion pneumothorax, in terms of blood transfusion, and other postoperative complications. Postoperative whole blood replacement was higher in Group 2 ($p=0.002$).

Conclusion: In off-pump heart surgery patient groups that do not have a high risk of bleeding, follow-up can be done without inserting an intercostal chest tube as a result of good bleeding control.

Keywords: Beating heart, chest tube, Jackson-Pratt drain, pain.

Cardiovascular diseases are still among the most important causes of mortality and morbidity. The frequency of coronary artery bypass grafting operations, which is the last stage in the treatment of this disease group, is increasing day by day. After cardiac surgery, there may be pain in the sternotomy area and chest where the chest tubes are placed, which may affect the respiratory physiotherapy of the patients. Therefore, control and reduction of pain are crucial to respiratory care, cough, early ambulation, and strengthening deep breath, which is critical to pulmonary recovery.[1-3] The location of the drainage catheters is, therefore, crucial. The removal of chest tubes provides significant reductions in the severity of pain.[4] However, drain placement is necessary after these surgeries to drain the blood from the surgically traumatized areas of the patients, particularly the areas where the internal mammary artery is removed. Nonetheless, due to their firm and rigid structure, conventional chest tubes are capable of restricting postoperative breathing exercises for patients and thereby increasing hypoventilation and atelectasis. It is also thought that it may increase the use of analgesic agents.[5]

Due to their structure, the use of smaller and more flexible silicone drains can be as effective as larger

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and firm drains.[6] These drains are clog-resistant and cause less patient discomfort with their small size and flexibility. In addition, an earlier study showed that the incidence of pericardial effusion, tamponade, and postoperative atrial fibrillation was reduced compared to conventional large drains.[7] This study aimed to evaluate whether postoperative pain level changes and whether complications such as effusion and pneumothorax that require intervention arise due to the drainage placed in the thorax cavity, either intercostal or subxiphoidal.

PATIENTS AND METHODS

This prospective study was performed using two different methods of drainage systems in patients with isolated coronary artery disease who were operated at the Abant İzzet Baysal University İzzet Baysal Training and Research Hospital between January 2018 and December 2018. The patients included in the study were divided into two groups (Groups 1 and 2) and operated by the same surgical team. The groups were determined by drawing lots. The group of the patients was recorded only by the surgical team. The exclusion criteria were as follows: patients requiring additional intervention other than coronary bypass; patients over 80 years of age; patients in which the internal mammary artery was not utilized for various reasons during the operation; patients who had to be returned to on-pump surgery for hemodynamic reasons during the operation; patients with chronic renal failure receiving dialysis treatment; patients who were taken to the operation urgently and who used high doses of anticoagulants or antiaggregants. Initially, 135 patients were included in the study. However, six patients were excluded from the study since they did not attend the postoperative controls. Thus, a total of 129 patients (100 males, 29 females; mean age: 62.9±8.5 years; range, 44 to 82 years) were evaluated, with 64 patients in Group 1 and 65 patients in Group 2.

Anesthesia and surgical technique

Standardized drugs (midazolam, rocuronium, fentanyl, and propofol) were administered to all patients as anesthetic drugs by the same anesthesia team at our institution. All patients were operated on by median sternotomy. The internal mammary artery was used in all patients. The saphenous vein was used for other vessels according to the number of diseased vessels. Off-pump surgery was performed in all patients. After appropriate heparinization (heparin at a dose of 1 mg/kg; activated clotting time was kept at >300 sec), distal anastomoses were performed with octopus support, and proximal anastomoses were performed with a side clamp. After standard bleeding controls, one no. 32 Fr drain and one Jackson-Pratt drain (extending between the posterior part of the heart and the pericardium) were placed to the mediastinum of patients in Group 1. No thorax drain was placed in this group of patients. In Group 2, one no. 32 Fr drain was placed in the mediastinum and one no. 36 Fr drain in the left thorax (through the fifth or sixth intercostal space in the middle axillary region). Heparin neutralization was performed with protamine. The mediastinum was routinely closed in all of the patients in the same way.

Postoperative follow-up

All patients were transferred to the intensive care unit. Pneumothorax was checked by posteroanterior chest radiographs. All patients were extubated at the appropriate time after routine intensive care follow-up. The pain assessment of the patients in the surgical area was started 1 h after the extubation and evaluated every 6 h using a verbal pain category scale indicated in Figure 1, and the scores were recorded.[8] Nonsteroidal pain relievers were administered to patients who responded as feeling a pain level of 2 or 3. Narcotic analgesics (tramadol 50 mg) were administered to patients who indicated a pain level of 4 or 5.

Intensive care follow-up was performed to the same standards. Antiaggregant and anticoagulant postoperative treatment was conducted similarly. Drains were pulled in the last 12 h if there was less than 100 mL of drainage. The first posteroanterior chest radiographs were obtained after the operation. Chest radiographs were renewed

Mild	Discomforting	Distressing	Horrible	Excruciating
1	2	3	4	5

Figure 1. Verbal category scale.[8]

daily until discharge. After the patients were discharged, chest radiographs were taken on the seven- and 30-day controls to see if there was any effusion requiring intervention in the left thorax. Posteroanterior chest radiographs were obtained at discharge, and both posteroanterior and left lateral radiographs were taken in controls after discharge since they were able to show less amount of fluid. Thorax ultrasonography was performed on patients with suspicious appearance on direct radiographs as it is more sensitive. Consultations from the thoracic surgery department were conducted for the patients with effusion findings to discuss whether to intervene. In case of need, pleural drainage procedures were performed by the same surgical team.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Data were reported as mean ± standard deviation (SD), median (interquartile range), or frequency (percentage). The independent sample t-test, chi-square test, Fisher exact test, Mann-Whitney U test, GLM, and repeated analysis of variance measurements were used. The statistical significance level was accepted as $p<0.05$.

RESULTS

The rate of chronic obstructive pulmonary disease was significantly higher in Group 2. The history of a cerebrovascular event was more common in patients in Group 1. There was no significant difference between the other variables (Table 1).

Preoperative laboratory data were compared between the groups. The albumin value was significantly higher in Group 1, and the calcium value was significantly higher in Group 2. There was no significant difference in other baseline values (Table 2).

Effusion requiring drainage was detected in two patients at the first control after discharge in Group 1. In the same group, one patient had minimal pneumothorax without intervention in the left thorax. In Group 2, two patients underwent percutaneous thoracentesis due to significant pleural effusion at the first outpatient control, although there were no patients with pneumothorax. Frequency of these complications was not statistically significant between the two groups.

Although there were no significant differences in the amount of postoperative drainage and

Table 1
Preoperative demographic characteristics and clinical data

	Group 1 (n=64)			Group 2 (n=65)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			61.6±9.3			63.3±7.3	0.257
Sex							0.558
Male	51	79.7		49	75.4		
Female	13	20.3		16	24.6		
Diabetes mellitus	32	50		24	36.9		0.134
Hypertension	36	56.2		40	61.5		0.541
COPD	1	1.6		9	13.8		**0.009**
Chronic renal failure	0	0		1	1.5		0.504
Peripheral artery disease	7	10.9		2	3.1		0.078
Cigarette	28	43.8		23	35.4		0.331
Cerebrovascular event	6	9.4		0			**0.013**
Hyperlipidemia	8	12.5		12	18.5		0.350
Ejection fraction			51.78±8.88			53.72±7.06	0.351
FEV1/FVC (%)			76.47±3.65			75.57±4.40	0.227

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; FEV1/FVC: Forced expiratory volume in one second/forced vital capacity.

Table 2
Preoperative laboratory values

	Group 1 (n=64)	Group 2 (n=65)	
	Mean±SD	Mean±SD	*p*
White blood cell (K/mm^3)	8.32±2.32	8.14±2.03	0.906
Hemoglobin (g/L)	13.53±1.58	13.83±1.34	0.260
Hematocrit (%)	41.39±4.84	41.43±4.30	0.960
Platelet (K/mm^3)	231.36±73.27	226.70±56.29	0.849
Blood urea nitrogen (mmol/L)	38.92±13.61	35.34±8.73	0.225
Creatine (µmol/L)	0.94±0.21	0.95±0.24	0.670
Calcium (mmol/L)	9.19±0.47	8.90±1.08	**0.014**
Albumin (µmol/L)	4.04±0.33	4.25±0.57	**0.012**
Protrombin time (sec)	11.50±0.86	11.73±0.90	0.145
Partial thromboplastin time (sec)	26.42±4.91	24.49±2.96	**0.011**
International normalized radio	0.98±0.07	1.03±0.08	**0.001**

SD: Standard deviation.

intraoperative and postoperative blood transfusion, the need for fresh frozen plasma and fresh whole blood in the postoperative period was significantly higher in Group 2 (Table 3). Operation time, postoperative extubation time, postoperative atrial fibrillation frequency, and discharge times were similar in both groups. The number of vessels undergoing anatomic surgery and the length of intensive care unit stay were significantly higher in Group 1 (Table 4). The verbal category scale for the pain assessment of the patients was found to be significantly higher in those in Group 2 in all evaluation periods in the first 48 h (Table 5). Based on the pain rating scale, nonsteroidal analgesia and

Table 3
Blood transfusion and drainage between groups

	Group 1 (n=64)	Group 2 (n=65)	
	Mean±SD	Mean±SD	*p*
Intraoperative			
Plasma	2.33±0.714	2.77±0.425	**0.001**
Whole blood	0.03±0.175	0.15±0.364	0.113
Erythrocytes	0.25±0.563	0.31±0.465	0.188
Postoperative			
Plasma	0.28±0.723	0.40±0.703	0.134
Whole blood	0.03±0.175	0.22±0.414	**0.002**
Erythrocytes	0.59±0.771	0.46±0.588	0.496
Postoperative			
Day 1 drainage	409.84±197.930	394.31±159.099	0.806
Day 2 drainage	152.81±104.76	142.38±64.742	0.867
Day 3 drainage	24.60±51.48	12.50±30.86	0.275
Total drainage	608.75±320.548	551.08±197.271	0.622

SD: Standard deviation.

Table 4
Operational and postoperative follow-up parameters between groups

	Group 1 (n=64)			Group 2 (n=65)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Operation time (h)			4.10±0.68			4.03±0.68	0.617
Number of vessels (n)			3.81±1.13			3.20±0.93	**0.001**
Atrial fibrillation	17	26.56		18	27.69		0.345
Extubation times (h)			6.07±1.52			5.98±1.14	0.794
Intensive care exit times (h)			61.98±25.329			48.63±10.268	**0.003**
Discharge time (h)			5.69±1.20			5.57±1.43	0.520
Pleural effusion	2	3.1		2	3.07		
Pneumothorax	1	1.56		-	-		

SD: Standard deviation.

narcotic analgesia applications were significantly higher in Group 2 (Table 6).

DISCUSSION

In patients undergoing open heart surgery, a drainage system is necessary to prevent tamponade due to accumulation in the pericardial area and to reduce pleural effusions. The chest drainage system did not change for years due to the presence of severe complications. Although there is a need for tubes to provide drainage, it is also known that these tubes are a significant source of pain in the postoperative period. It may also limit patient activity and cause uneasiness in coughing and deep breathing. This can ultimately cause inadequate expansion of the thoracic cavity and respiratory infections.[9] Studies have not focused on reducing these drains but rather on their consequences. There are studies to reduce the pain caused by drains and the pain that occurs when they are removed.[10] In the present study, we concluded that the need for postoperative chest drain placement, known as the traditional doctrine of open heart surgery, can be eliminated with a conventional drain and Jackson-Pratt drain placed in the mediastinum, particularly in off-pump coronary bypass surgery.

In a study conducted by Guden et al.[11] in 2012, it was shown that both the subxiphoid and intercostal tract could be used to insert a chest tube. Although there are early studies on different locations of the chest tube, no studies have been conducted on not placing drains into the thoracic cavity. Pericardial

Table 5
Comparison of pain scores between groups

	Group 1 (n=64)	Group 2 (n=65)	
	Mean±SD	Mean±SD	*p**
After extubation (h)			
1st	2.23±0.496	2.83±0.525	0.001
6th	1.84±0.672	2.81±0.564	0.001
12th	1.66±0.511	2.71±0.455	0.001
18th	1.27±0.445	2.37±0.548	0.001
24th	1.17±0.380	2.14±0.503	0.001
48th	1.11±0.315	1.90±0.530	0.001

SD: Standard deviation; * Mann Whitney U test.

Table 6
Postoperative pain relief between the groups

	Group 1 (n=64)		Group 2 (n=65)		
	n	%	n	%	*p**
After extubation (h)					
1st	17	26.6	50	79.4	**0.001**
Narcotic analgesia (h)					
6th	10	15.6	47	74.6	**0.001**
12th	1	1.6	43	68.3	**0.001**
18 th	0	0	25	39.7	**0.001**
24th	0	0	12	19.0	**0.001**
48th	0	0	6	9.5	**0.013**
After extubation (h)					
1st	45	70.3	11	17.5	**0.001**
Non steroid analgesia (h)					
6th	34	53.1	17	27.0	**0.001**
12th	40	62.5	17	27.0	**0.001**
18th	17	26.6	36	57.1	**0.001**
24th	11	17.2	45	71.4	**0.001**
48th	7	10.9	44	69.8	**0.001**

SD: Standard deviation; * Pearson chi-square.

tamponade is the most feared complication after cardiac surgery. We were able to execute the study since we used mediastinal drains to eliminate this risk.

In a study by Frankel et al.,[12] no significant difference was evident in intensive care follow-ups between the patients who were using classical chest tubes and flexible silastic drains. In our study, although there was a significant difference in terms of length of stay in the intensive care unit in favor of the patients in Group 1, it did not affect our results since it was not one of the main evaluation points of this study.

There was a significant difference in pain scores and analgesia needs, particularly in the postoperative follow-up period and until the drains were removed. There was a significant decrease in pain in Group 1 starting at the first hour after the intubation and in the type and amount of analgesia performed. In a study conducted by Bjessmo et al.,[13] no significant difference was reported in the assessment of pain with the use of two different drains. There are contradictory results in the literature on this subject. Some studies support the results of our study.[14,15] Although there was a significant increase in the duration of intensive care unit stay in Group 1, significant improvements were observed in patients in Group 2 in terms of treatment compliance, mobilization, and compliance with respiratory physiotherapy exercises. These data suggest that this is due to low levels of pain and analgesic needs of patients. Pulmonary hypoventilation findings may occur due to decreased pulmonary function of patients due to trauma in bone and muscle during surgery.[16] The location of the drain to be placed in the thoracic cavity has been well studied, and in our study, effusion, which required thoracentesis on the fifth postoperative day, was detected only in two patients after the drainage was not placed in the thorax cavity. Only one patient developed left minimal pneumothorax that did not require any intervention and regressed in the follow-up. In the same way, the necessity of thoracentesis was determined and applied to the two patients in the first group after discharge. This suggests that there is no significant difference in pleural complications. Our results are not congruent with a priori knowledge of the necessity of a thoracic tube in classical surgical teaching.

Pleural effusion after cardiac surgery may be due to many causes.[17] However, it is mainly caused by leaks due to trauma in the inner wall of the thoracic wall triggered by the removal of the internal mammary artery. Our study does not focus on the causes of effusion but on whether there is a difference between drain types and accumulated fluid. It is suggested that the absence of a significant hemothorax is due to the fact that there is no adverse effect on the coagulation system in patients due to off-pump surgery and good bleeding control within the operation.

In a study conducted in 2002, no significant difference was reported between flexible silastic drains and classical large drains in terms of pericardial tamponade and pleural effusion.[15] In another study by Moss et al.,[18] similar effusion tamponade results were obtained for both drainage methods. In our study, there was no significant difference in terms of pleural effusion and pericardial tamponade despite the absence of thorax drainage.

One of the common problems after open heart surgery is cardiac arrhythmias with predominantly atrial fibrillation.[19] In the first three days after surgery, there is a significant increase in atrial fibrillation formation.[20] Some studies indicated that the development of atrial fibrillation leaded to a prolonged postoperative intensive care follow-up and discharge times.[21,22] In our study, although the development of atrial fibrillation was higher in percentage, particularly in Group 2, there was no difference between the groups. Since other factors that play a role in the development of atrial fibrillation were not fully compared in our study, it is difficult to make a conclusive comment based only on the types of drains. The fact that there was no significant difference between the two groups in terms of operation times, postoperative intubation times, postoperative stroke, and discharge times made it easier for us to compare postoperative pain and pleural complications.

In Group 2, higher activated prothrombin time and international normalized ratio values in the preoperative period caused an increase in intraoperative fresh frozen plasma and postoperative fresh whole blood transfusion. This situation is incongruent with the studies reported in the literature. Since other parameters were not studied in terms of bleeding, no definitive interpretation could be remarked regarding this condition.

There were several limitations in the present study. The first limitation was the detection of the amount of postoperative effusion by chest radiography, which is known for being not sensitive to effusions of less than 200 mL. This evaluation was first performed by the cardiac surgery team and not by the radiology team. The second limitation was that the follow-up of the patients was not completely blinded, as the same team conducted the follow-ups. The effect of other sources of pain, such as median sternotomy and saphenous incision location, could not be included in the study. In our clinic, a 36 Fr tube was used for the thorax region as a routine procedure. The size and type of chest tubes (36 Fr tube) may have affected the effectiveness of pleural drainage, pain sensation, and associated morbidities.

In conclusion, drains are crucial for patient monitoring in cardiac surgery. We believe that, particularly in off-pump heart surgery patients who do not have a high risk of bleeding, follow-up can be done without inserting an intercostal chest tube if good bleeding control is provided. More comprehensive studies are needed on this subject.

Ethics Committee Approval: The study protocol was approved by the Abant İzzet Baysal University Clinical Researches Ethics Committee (date: 28.12.2017, no: 2017/201). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Cardiovascular Surgery and Interventions

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Acute reperfusion treatment in cases with ST-elevation myocardial infarction and peripheral neutrophilia

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ABSTRACT

Objectives: The study aimed to assess the correlation between neutrophil count at admission and during the short-term follow-up period with clinical outcomes in individuals presenting with ST-elevation myocardial infarction (STEMI).

Patients and methods: This prospective study was conducted between March 2010 and September 2010. Seventy-two patients (58 males, 14 females; mean age: 67±12 years; range, 50 to 89 years) diagnosed with acute coronary syndrome presenting with STEMI were included in the study. Complete blood count, serum glucose, urea, creatinine levels, and glomerular filtration rate were assessed in patients at 0, 4, 24, and 48 h. Patients were stratified according to the Killip-Kimball classification. Adverse clinical outcomes were defined as death, reinfarction, and cerebrovascular disease.

Results: Adverse clinical outcomes were significantly higher in patients with higher age and Killip-Kimball scores ($p=0.04$, $p<0.01$). A correlation was identified between the white blood cell (WBC) count at 48 h ($p=0.04$) and the neutrophil count at all time points with adverse clinical outcomes ($p<0.05$).

Conclusion: In our study, a correlation was determined between WBC and neutrophil counts and the rates of in-hospital mortality and adverse clinical outcomes in individuals presenting with acute STEMI. Elevated neutrophil count assessed upon admission to the hospital and during short-term follow-up may be utilized to identify high-risk patients.

Keywords: Acute coronary syndrome, Killip-Kimball Classification, neutrophil count, ST elevation myocardial infarction.

Acute coronary syndrome (ACS) is a group of clinical syndromes caused by acute myocardial ischemia. It can lead to heart failure, arrhythmias, and even sudden death. It is recognized as a prominent factor contributing to disability and mortality on a global scale.[1] Neutrophils, which are innate immune cells within the body, play a crucial role as the initial barrier of protection against pathogens. Stimulation of neutrophils can trigger various pathological processes, including inflammation.[2] It has been demonstrated that systemic inflammatory mediators play a significant role in atherosclerosis and coronary artery disease.[3] The elevation of circulating white blood cells (WBCs), nonspecific markers of inflammation, can lead to adverse clinical outcomes in coronary artery disease, including ST-elevation myocardial infarction (STEMI).[4] It has been reported that particularly neutrophils are associated with extensive infarct areas, worse angiographic outcomes, and adverse short-term prognosis in STEMI.[5] Neutrophils are known to trigger coagulation, increase microvascular permeability, and mediate ischemia reperfusion injury in ACS.[6]

According to current guidelines, the gold standard treatment following STEMI is percutaneous coronary intervention.[7] Acute reperfusion therapy is preferred in situations where percutaneous coronary intervention cannot be performed. It has been shown that early reperfusion therapy improves outcomes in patients with STEMI.[8]

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The relationship between neutrophil counts and angiographic indexes during reperfusion is not clear. The objective of this study was to assess the correlation between neutrophil count at admission and during the short-term follow-up period with clinical outcomes in patients diagnosed with STEMI.

PATIENTS AND METHODS

This prospective study was conducted at the Eskişehir Osmangazi University Faculty of Medicine between March 2010 and September 2010. Seventy-two patients (58 males, 14 females; mean age: 67±12 years; range, 50 to 89 years) diagnosed with ACS and presenting with STEMI upon admission to the emergency department were included in the study. A STEMI was defined according to the criteria outlined in the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction.[9] Patients under 18 years of age, pregnant individuals, those with active malignancy or active infection within the last three months, and patients with multiple organ failure were excluded from the study. Adverse clinical outcomes during follow-up included death, reinfarction, and cerebrovascular disease (CVD).

The Killip-Kimball classification (KC) was developed by Killip and Kimball[10] to stratify patients into four groups according to clinical criteria. In the present study, patients were divided into two groups according to the KC: Group 1 consisted of 60 (83.3%) patients with KC-I (no signs of congestion) or KC-II (S3 heart sound and basal rales on auscultation, and Group 2 consisted of 12 (26.7%) patients with KC-III (acute pulmonary edema) or KC-IV (cardiogenic shock).

Complete blood count was performed for all patients at 0, 4, 24, and 48 h after admission. Hemoglobin, hematocrit, WBC count, and neutrophil count data were compared. Analysis was conducted using the Siemens Advia 2120i device (Siemens Healthcare Diagnostics Inc., Tarrytown, USA). Venous blood samples were obtained between 8:00 and 9:00 in the morning following an overnight fasting of 8 to 10 h. Serum glucose, urea, and creatinine levels were analyzed using the Cobas Integra 400 plus device (Roche Diagnostics, Basel, Switzerland). The glomerular filtration rate (GFR) value was determined using the Modification of Diet in Renal Disease criteria.

Statistical analysis

The data were analyzed using IBM SPSS version 19 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequency. For the comparison of continuous variables showing normal

Table 1
Clinical characteristics and risk factors of patients according to adverse clinical outcomes

	All patients (n=72)			Patients without adverse clinical outcome (n=60)			Patients with adverse clinical outcome (n=12)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			67±12			58.8±15			69±10	**0.01**
Sex										
Male	58	80.6		50	83.3		8	66.7		0.386
Hypertension	35	48.6		29	48.3		6	50		0.579
Family history of coronary artery disease	15	13.9		9	15		6	26		0.716
Smoke	31	43.1		29	48.3		2	16.6		**0.04**
Diabetes mellitus	28	38.9		21	35		7	58.3		0.435
Hyperlipidemia	14	19.4		13	21.6		1	8.3		0.835
KC I-II	60	83.3		57	95		3	25		**<0.01**
KC III-IV	12	26.7		3	5		9	75		**<0.01**

SD: Standard deviation; KC: Killip-Kimball classification.

distribution, Student's t-test was used, while for those not showing normal distribution, the Mann-Whitney U test was employed. For the comparison of categorical variables, the chi-square test was used. A *p*-value <0.05 was considered statistically significant.

RESULTS

Primary percutaneous coronary intervention was performed in 52 (72.2%) of the patients included in the study. Among the patients, 35 (48.6%) had hypertension, 15 (20.83%) had a family history of coronary artery disease, 28 (38.9%) had diabetes mellitus, 31 (43.1%) were smokers, and 14 (19.4%) had hyperlipidemia. Adverse outcomes were identified in 12 (16.7%) patients. Among these, reinfarction occurred in three (4.2%) patients, CVD in two (2.8%) patients, and death in seven (9.7%) patients. In the two patients who developed CVD, the etiology was ischemic in both cases, and no deaths were observed during follow-up (Table 1).

In the evaluation according to the presence of adverse outcomes, A positive relationship was found within the context of age between the two groups (p=0.01), while a negative relationship was observed within the context of smoking status (p=0.04). In patients with KC III-IV upon admission to the coronary intensive care unit, adverse clinical outcomes were significantly higher (p<0.01, Table 1).

White blood cell and neutrophil counts were assessed at 0, 4, 24, and 48 h. A relationship was observed between WBC count at 48 h (p=0.04) and neutrophil count at all time points with adverse clinical outcomes (p<0.05, Table 2).

The relationship between clinical characteristics, hematological parameters, KC scores, and mortality within adverse clinical outcomes was evaluated. A significant relationship was found between advanced age, elevated WBC count at 48 h, elevated neutrophil count at all time points, and mortality (p<0.05). Out of the seven deceased patients, six were in Group 2, while only one patient was in Group 1 (p<0.01, Table 3).

When those with and without adverse clinical outcomes were compared, a positive relationship was observed between elevated blood sugar and creatinine levels, and a negative relationship was observed with GFR (p<0.01, Table 3).

When the patients were compared based on normal and elevated neutrophil levels, neutrophil levels were significantly higher in patients with higher age, creatinine, and KC scores (Table 4).

DISCUSSION

Acute coronary syndrome is one of the most significant contributors to cardiovascular morbidity and mortality.[11] Inflammation plays a significant role in the development of ACS, according to a study.[12]

Table 2
White blood cell and neutrophil parameters of patients according to adverse clinical outcomes

	Patients without adverse clinical outcome (n=60)	Patients with adverse clinical outcome (n=12)	
	Mean±SD	Mean±SD	*p*
0th hour white blood cell count	14.400±2.900	15.700±6.600	0.538
4th hour white blood cell count	16.300±3.600	15.500±5300	0.975
4th hour white blood cell count	14.700±3.100	16.800±5.900	0.753
48th hour white blood cell count	11.000±3.980	18.800±2.110	0.04
0th hour neutrophil count	8.988±1.100	12.200±1.770	0.01
4th hour neutrophil count	9.688±528	13.100±1.530	0.01
24th hour neutrophil count	8.510±520	14.300±1.570	0.04
48th hour neutrophil count	7.445±520	16.200±1.900	0.02

SD: Standard deviation.

Table 3
Hematological parameters, laboratory data, and KC classification in deceased patients

	Died (n=7)			Alive (n=65)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			71.5±9.8			59.5±15	0.01
Sex							
Male	5	71.4		53	81.5		0.579
0th hour white blood cell count			18.400±6.193			14.193±7.250	0.538
4th hour white blood cell count			17.910±4.410			15.500±5300	0.975
24th hour white blood cell count			18.328±4.900			14.680±2.760	0.753
48th hour white blood cell count			21.100±2.455			11.300±4.470	0.007
0th hour neutrophil count			14.042±2.437			9.041±3.681	0.01
4th hour neutrophil count			15.428±3.770			9.681±4.081	0.01
24th hour neutrophil count			15.742±4.663			8.792±4.362	<0.01
48th hour neutrophil count			18.542±5.543			7.857±4.554	<0.01
Glukoz (mg/dL)			301±181.2			166±99.9	<0.01
Creatinine (mg/dL)			1.90±1.49			1.03±0.64	<0.01
eGFR (mL/min/1.73 m^2)			65±12			50±14	<0.01
KC I-II	1	9.3		59	90.7		<0.01
KC III-IV	6	85.7		6	9.2		<0.01

KC: Killip-Kimball classification; SD: Standard deviation; eGFR: Estimated glomerular filtration rate.

Table 4
Comparison of clinical findings and laboratory values according to neutrophil counts

	Normal neutrophil count			Increased neutrophil count			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			59±6.3			65±8.7	0.03
Sex							
Male	26			32			0.584
Creatinine (mg/dL)			1.13±0.94			1.70±1.59	0.005
eGFR (mL/min/1.73 m^2)			65±7.8			53±6.4	0.003
KC I-II	35	58.3		25	41.7		0.384
KC III-IV	2	16.6		10	83.4		0.001

KC: Killip-Kimball classification; SD: Standard deviation; eGFR: Estimated glomerular filtration rate.

In this study, a direct correlation was observed between an increase in the WBC, particularly neutrophil count, at the time of diagnosis and during follow-up and adverse clinical outcomes in patients presenting to our emergency department due to STEMI. Adverse clinical outcomes were characterized as mortality, recurrent infarction, and CVD. In our study, the neutrophil count was significantly higher in those who were older and had high KC scores and creatinine levels. Patients with adverse clinical outcomes were older and had higher KC scores. In this group of patients, the neutrophil count was significantly elevated at the time of diagnosis and throughout the short follow-up period. Similarly, when it comes to their relationship with mortality, mortality was higher in those with high neutrophil counts, KC scores, and creatinine.

Acute myocardial infarction (AMI) is a systemic inflammatory disease triggered by acute inflammation. The severity of inflammation correlates with the extent of myocardial infarction. In patients with elevated WBC and neutrophil counts during the course of AMI, a larger infarct size was observed.[13] In the study conducted by Tavares et al.,[14] individuals with higher neutrophil ratios were found to be older, had higher KC scores, had a higher rate of smoking, exhibited more impaired renal function, and experienced a higher rate of hospitalization for all causes. On the other hand, according to a study comparing neutrophil counts and infarct size in patients with AMI, individuals with high neutrophil counts at admission statistically had a significantly larger infarct area.[15] In another study involving 363 patients with AMI, it was observed that individuals with high neutrophil and WBC counts had significantly more extensive infarct areas along with a higher incidence of adverse cardiac endpoints.[16] In our study, adverse clinical outcomes were more prevalent in elderly patients and those with KC scores of III-IV. Similar to the study conducted by Mello et al.,[17] it was observed that mortality rates increased with higher KC scores and age following ACS. The reason for the association between elevated neutrophil counts post STEMI and adverse clinical outcomes may be attributed, as demonstrated in previous studies, to the role of leukocytes, particularly neutrophils, in plaque rupture, reperfusion injury, and remodeling processes in ACS.[18] Furthermore, neutrophils may trigger the occurrence of reinfarction by facilitating platelet neutrophil interactions, thrombus formation, and the continuation of coagulation through the membrane attack complex-1 (CD11b-CD18) pathway.[19] The high neutrophil percentage may also be independently associated with damage occurring in microvascular perfusion. Interactions between neutrophils, platelets, and endothelium in ACS can also lead to cytokine release, which may contribute to microvascular dysfunction.[20] In a study involving 160 patients with non-ST-elevation ACS, it was found that cases with high neutrophil counts upon admission to the hospital had a statistically higher incidence of death, acute heart failure, and recurrent myocardial infarction.[21] In our study, patients in the group with high neutrophil counts had higher creatinine levels and lower GFR. Similar to our study, in a study conducted, impaired renal function resulted in increased mortality and prolonged intensive care unit stay in patients undergoing reperfusion therapy after STEMI.[22]

The most significant limitation of the study is the small number of participants. Additionally, two different reperfusion strategies were applied to the patients. Pharmacological reperfusion was attained through the administration of thrombolytic therapy, whereas mechanical reperfusion was achieved through primary percutaneous coronary intervention. These two methods have different effects on systemic inflammation. In our study, the majority of patients underwent primary percutaneous coronary intervention treatment.

In conclusion, a correlation was determined between WBC and neutrophil counts and the rates of in-hospital mortality and adverse clinical consequences in individuals presenting with acute STEMI. There are numerous studies conducted on the WBC count in patients diagnosed with ACS, including AMI. However, the number of studies examining the relationship between neutrophil count and adverse clinical outcomes is limited. Elevated neutrophil count assessed upon admission to the hospital and during short-term follow-up may be utilized to identify high-risk patients.

Ethics Committee Approval: The study protocol was approved by the Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (date: 21.05.2010, no: PR-10-03-19-09). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Our experience with carotid endarterectomy under cervical plexus block in a patient with an indication for heart transplantation

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ABSTRACT

Carotid endarterectomy is among the best treatment methods for patients with severe carotid stenosis who have experienced transient ischemic attacks. Performing it under cervical plexus block reduces anesthesia-related complications during the perioperative periods in patients for whom general anesthesia carries high risks. Additionally, it facilitates the early detection of intraoperative neurological complications. Herein, we shared our experience on a 56-year-old male patient who was at high risk for general anesthesia due to various comorbidities and underwent carotid endarterectomy under cervical plexus block. Cervical plexus block is a method that can be preferred in carotid endarterectomy due to reduced costs and the rapid detection of neurological complications during the operation.

Keywords: Carotid endarterectomy, cervical plexus block, local anesthetics.

Cerebrovascular diseases, along with malignancies and cardiac diseases, are among the leading causes of death. Carotid artery stenosis accounts for approximately 25% of all ischemic cerebrovascular events, and early diagnosis and treatment can reduce morbidity and mortality. Carotid endarterectomy (CEA) remains the gold-standard treatment method for symptomatic patients with severe carotid stenosis (>70% stenosis).[1]

Carotid endarterectomy surgery can be performed under general or regional anesthesia.[2] Regional anesthesia is becoming increasingly common in this surgery due to its ability to allow for consciousness, sensation, speech, and motor tracking during the intraoperative period, enabling early detection and intervention in cerebrovascular events that may occur within the case. Additionally, in elderly patients with low cardiac or pulmonary capacity, regional anesthesia is preferred for the higher risk of general anesthesia. Herein, we shared our experience of CEA surgery under deep-superficial cervical plexus block on a patient with an American Society of Anesthesiologists (ASA) physical status score of 4.[3]

CASE REPORT

A 56-year-old male with a known history of diabetes mellitus, hypertension, congestive heart failure, and coronary artery disease who had experienced an ischemic cerebrovascular event six years prior presented to the emergency department with complaints of slurred speech for the past two days and weakness in the right arm. Upon arrival, diffusion-weighted magnetic resonance imaging in the emergency department revealed diffusion restriction in the deep cortex of the left lateral ventricle, prompting investigation and treatment planning for cerebrovascular disease at the neurology ward. Upon physical examination on admission, the patient was conscious with dysarthric

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speech. Weakness was noted in the right upper extremity, with a first-degree paresis.

A craniocervical computed tomography angiography performed during hospitalization revealed mixed-type atheromatous plaques extending to the proximal segment of the internal carotid artery at both common carotid artery bifurcation levels, with a 90% stenosis observed in the proximal right internal carotid artery lumen.

The patient was evaluated for cardioembolic events, and the electrocardiogram (ECG) showed a first-degree atrioventricular block and an incomplete left bundle branch block. Echocardiography revealed an ejection fraction of 20%, global hypokinesis, and moderate mitral regurgitation, with a systolic pulmonary artery pressure of 35 mmHg. Under these conditions, the patient was evaluated as a heart transplantation candidate[4] but was not placed to the heart transplantation list due to carotid and peripheral artery diseases.

Diuretics were initiated for bilateral pleural effusions. The patient received a 3% sodium chloride infusion for hyponatremia (sodium: 117 mmol/L). Since an acute phase response was observed (C-reactive protein: 88 mg/L), the patient was assessed by infectious diseases for suspected infection, and piperacillin-tazobactam was initiated due to a suspected infective diabetic foot ulcer. The patient was scheduled for surgery and was evaluated preoperatively as ASA 4 due to additional comorbidities. A cervical plexus block was planned for the patient.

The patient's preoperative arterial blood pressure was 138/90 mmHg, heart rate was 87 bpm, and peripheral oxygen saturation (SpO_2) was 93%. Invasive blood pressure, oxygen saturation, temperature, ECG, patient state index (PSI), and near-infrared spectroscopy (NIRS) monitoring were conducted. Under sterile conditions, C2-C4 transverse processes were identified for the purpose of a right deep cervical plexus block. To each of the three points, local anesthetics were injected (2.5 mL of 0.5% bupivacaine and 1 mL of 2% lidocaine). Afterward, the superficial cervical plexus block was administered with 10 mL of local anesthetics. Adequate sensory block was confirmed in the planned surgical area, and the patient was handed over for surgery.

After the block, intravenous dexmedetomidine infusion (0.2 mcg/kg/h) was started for sedation. At the beginning of the surgery, NIRS readings were 34/36 (right/left). The patient lying supine was placed in a left hyperextension position, and the procedure commenced after surgical site preparation. Throughout the operation, consciousness was monitored, and motor functions were assessed.

Fifteen minutes after the start of surgery, 5000 IU of heparin was administered intravenously, and 3 min later, the activated clotting time was measured as 233. After 15 min of cross-clamp time, the right CEA (with the conventional technique) was completed, and after hemostasis, a drain was placed. The skin incisions were closed in accordance with the patient's anatomy. There were no changes in consciousness or motor function during the operation, and there was no drop in NIRS values. Sedation levels were adjusted according to PSI levels.

During the intraoperative period, there was no need for vasopressor agents, and there were no sudden bradycardia or hypotension events. At the end of the operation, NIRS readings were 45/35 (right/left). The patient was transferred to the intensive care unit (ICU) with an SpO_2 of 98% (under oxygen support), blood pressure of 148/88 mmHg, and a pulse rate of 81 bpm. The patient was monitored in the ICU overnight and transferred to the ward in the morning. The patient, who did not experience any complications, had the drain removed on the third postoperative day and was discharged.

DISCUSSION

While there are studies showing that there is no superiority among the anesthesia methods used for CEA,[5] the frequency of CEA performed under cervical plexus block is increasing nowadays due to its advantages such as allowing intraoperative consciousness monitoring, absence of recovery time in general anesthesia, increasing patient comfort, and reducing the hospital stay. The choice of anesthesia method can be determined by the clinic's experience, or in cases where general anesthesia is high risk, it can also be determined by considering the patient's benefit in reducing anesthesia-related complications.

Detecting immediate neurological signs during surgery performed with open consciousness and applying shunts to these patients can prevent unnecessary shunt use, thus reducing the frequency

of complications, such as stroke and vascular injury, that may arise from shunt application. In the GALA trial, a multicenter, controlled, randomized study, it was found that the use of regional anesthesia reduced the need for shunting from 43 to 14%.[5] However, in the same study, no significant difference was observed between regional anesthesia and general anesthesia in terms of perioperative death, stroke, or myocardial infarction. Nevertheless, there are studies indicating an increased risk of myocardial infarction in the general anesthesia group.[6] Neurological events occurred in 23 out of 310 patients, with a significant risk identified in those operated under general anesthesia.[7]

In this case, in addition to nerve block, sedation was provided to the patient with intravenous dexmedetomidine infusion to increase patient and surgeon comfort. As known, dexmedetomidine has anxiolytic, sedative, and analgesic effects, and its risk of respiratory depression is lower than other intravenous sedative agents. Dexmedetomidine improved the recovery of cognition after CEA, potentially due to reduced inflammation and enhanced brain-derived neurotrophic factor expression.[8] Due to the low hemodynamic effect of dexmedetomidine, there was no need for vasopressor agents at the sedation dose provided.

In conclusion, cervical plexus block for CEA is a method that can be preferred due to reduced costs and rapid detection of neurological complications that may occur during the intraoperative period. It significantly reduces the risk of intraoperative complications and ICU and hospital stays for patients. It is the preferred anesthesia method for patients at high risk for general anesthesia, provided there are no contraindications.

Patient Consent for Publication: A written informed consent was obtained from the patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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