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Cardiovascular Surgery and Interventions

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Association between coronary artery lesion severity in coronary computed tomography angiography and hemoglobin A1c in nondiabetic patients with chronic coronary syndrome

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ABSTRACT

Objectives: In this study, we aimed to investigate whether there is a relationship between coronary artery lesion severity detected on coronary computed tomography angiography (CTA) and the hemoglobin A1c (HbA1c) value in nondiabetic patients with chronic coronary syndrome (CCS).

Patients and methods: The retrospective observational study included 125 patients (64 males, 61 females; median age: 55 years; IQR, 46.5-63.0) who underwent coronary CTA with the diagnosis of CCS and applied between March 2020 and July 2022. Two groups were formed according to the severity of coronary artery lesion by coronary CTA: Group 1 (n=71), with <70% coronary lesion severity, and Group 2 (n=54), with >70% coronary lesion severity.

Results: The two groups were similar in terms of median age, (p=0.09) and male sex ratios (47% *vs.* 55%, p=0.47). The HbA1c value in Group 2 was statistically significantly higher than in Group 1 [5.89 (5.43-6.15) *vs.* 5.42 (5.1-5.8), p=0.001]. The HbA1c cut-off value was determined as 5.66. The ideal HbA1c cut-off value, calculated by the Youden index, had a sensitivity of 64% and a specificity of 63% in predicting the severity of coronary artery lesions in nondiabetic patients with CCS.

Conclusion: In nondiabetic patients with CCS, HbA1c is associated with the presence of severe CAD lesions detected in coronary CTA.

Keywords: Chronic coronary syndrome, coronary computed tomography angiography, HbA1c.

Coronary artery disease (CAD), characterized by atherosclerotic plaque accumulation in the epicardial arteries, is one of the leading causes of morbidity and mortality worldwide.[1] In the 2019 European Society of Cardiology (ESC) guidelines for chronic coronary syndrome (CCS), patients with stable angina pectoris or angina-equivalent symptoms/signs were defined as CCS (nonacute coronary syndrome), and diagnosis and treatment protocols were established for these patients.

During the diagnosis stage, noninvasive tests are recommended, and it is emphasized to decide on the pretest probability by evaluating cardiovascular risk factors (age, sex, hypertension, diabetes mellitus [DM], hyperlipidemia, smoking, and family history). Coronary computed tomography angiography (CTA), a noninvasive test, is the first recommended test when CAD cannot be excluded in symptomatic patients with clinical evaluation (ESC 2019 CCS guideline: Class I recommendation).[1]

Hemoglobin A1c (HbA1c) is one of the endogenous advanced glycation end products. In addition, HbA1c indicates the long-term average glycemic index. Hemoglobin A1c measurement does not require the fasting state of the patient or glucose loading to the patient; therefore, it is a parameter that provides higher reproducibility than fasting glucose and measurement of glycemia with a single sampling.[2] Known as an indicator of uncontrolled type 2 DM, HbA1c has been associated with echocardiographic left ventricular functions and with the frequency of infection after coronary

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artery bypass grafting in some studies.[3,4] It has been demonstrated that HbA1c is strongly associated with CAD and the diagnosis of DM and can be used as a biomarker of CAD.[2,5,6] The relationship between HbA1c and CAD severity in patients with DM is well understood, but the relationship between HbA1c levels and CAD severity in patients without DM is still controversial.[7,8] Hence, we aimed to investigate the relationship between HbA1c and CAD lesion severity in the nondiabetic adult population. We also tried to find the HbA1c cut-off value for risk stratification in nondiabetic patients with CCS.

PATIENTS AND METHODS

The retrospective study included 125 patients (64 males, 61 females; median age: 55 years; IQR, 46.5-63.0) who applied to the cardiology clinic of the Izmir Bakırçay University Çiğli Training and Research Hospital between March 2020 and July 2022. Demographic characteristics, such as age, sex, and comorbid diseases were recorded. Coronary CTA (256 multislice computed tomography) reports, which were reported by experienced specialists and taken under appropriate technical conditions, were reviewed, and information about the coronary artery lesion severity was recorded in the case report form. There were two groups formed according to the coronary CTA lesion severity: Group 1 (n=71), with a lesion severity <70%, and Group 2 (n=54), with a lesion severity >70%.

Patients younger than 18 years, patients with a history of DM or an HbA1c level above 6.5%, patients with a history of coronary artery bypass grafting, patients not in sinus rhythm, patients with severe liver failure, and patients with active malignancy were excluded from the study. Anemic patients (hemoglobin <10 g/dL) were excluded from the study. Therefore, it cannot be thought that it will affect the HbA1c value.

The blood pressures measured by manual sphygmomanometer at the outpatient admissions of the patients included in the study and the heart rates from the electrocardiograms taken at the outpatient admissions were noted from the hospital records. The body mass index was calculated as weight/height.[2]

Smoking and alcohol use of the patients were accepted if they were active users according to their verbal expressions. For the definition of hypertension, which is one of the comorbid diseases, a blood pressure >140/90 mmHg with repeated measurements or the use of oral antihypertensive drugs was taken as criteria. A glomerular filtration rate <60 mL/min was considered chronic renal failure, and total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >130 mg/dL or triglyceride >150 mg/dL was considered hyperlipidemia.

Statistical analysis

Data were analyzed using IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Normal distribution of numerical variables was examined using the Kolmogorov-Smirnov test. Numerical variables were expressed as median and interquartile range (IQR) and evaluated using Student's t-test. Categorical variables were reported as numbers and frequencies and evaluated using the Pearson chi-square test and Fisher exact test. If there was no normal distribution among the numerical variables, the Mann-Whitney U test was used. The HbA1c cut-off value was found by performing receiver operating characteristic (ROC) curve analysis. The cut-off value was determined according to the Youden index. A p value <0.05 was considered statistically significant.

RESULTS

The male sex ratio of the patients was 51%. The median body mass index was 25.5 (23.10-28.85) kg/m^2. No statistically significant difference was found between the two groups in demographic data, except for hypertension (Table 1). The rate of hypertension was higher in Group 2 compared to Group 1 (33% *vs.* 53%, p=0.03). The most common comorbid conditions (hypertension not included) were CAD (25%) and hyperlipidemia (24%). The rate of active smokers was similar between Group 1 and Group 2 (16% *vs.* 18%, p=0.81, Table 1).

One of the biochemical parameters, the high-density lipoprotein value was higher in Group 1 than in Group 2, but there was no statistically significant difference between groups (44 [38.15-51.32] *vs.* 40.5 [35-46.3], p=0.054). The median left ventricular ejection fraction (LVEF) value of the patients in the echocardiography was 60% (50-60%). The LVEF was higher in Group 1 than in Group 2 (60 [55-60] *vs.* 50 [45-60], p<0.001).

Table 1
Baseline characteristics and comorbid diseases of the study population

	Coronary lesion <70% (n=71)				Coronary lesion >70% (n=54)				Total (n=125)				
Variables	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Age (year)			54	43-61			56	50-63.25			55	46.5-63.0	0.09
BMI (kg/m^2)			25.8	23.5-28.7			25.4	22.92-29.02			25.5	23.10-28.85	0.51
Sex Male	34	47			30	55			64	51			0.47
SBP (mmHg)			130	120-143			140	129.75-155			135	125-149	0.1
DBP (mmHg)			75	65-85			80	70-90			80	70-90	0.09
Heart rate (min)			75	65-87			74	65-80			74	65-84	0.52
Smoking	12	16			10	18			22	17			0.81
Alcohol use	3	4			1	1			4	3			0.63
Hypertension	24	33			29	53			53	42			0.03
CAD	15	21			17	31			32	25			0.21
Hyperlipidemia	15	21			16	29			31	24			0.3
COPD	2	2			4	7			6	4			0.4
Asthma	5	7			2	3			7	5			0.69
CKD	4	5			7	12			11	8			0.2
PAD	2	2			5	9			7	5			0.23

IQR: Interquartile range; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; PAD: Peripheral artery disease.

Table 2
Biochemical and imaging findings

	Coronary lesion <70% (n=71)		Coronary lesion >70% (n=54)		Total (n=125)		
Parameters	Median	IQR	Median	IQR	Median	IQR	*p*
Urea (mg/dL)	18	11-27	17.25	12.75-32.1	18	11.45-28	0.14
Creatinine (mg/dL)	0.85	0.77-1.13	0.9	0.69-1.2	0.87	0.74-1.14	0.13
Na (mEq/L)	139	137-141	139	136.75-140	139	137-140	0.28
K (mEq/L)	4.2	3.9-4.53	4.22	4-4.6	4.2	3.96-4.60	0.28
Ca (mg/dL)	9	8.7-9.2	9	8.55-9.3	9	8.7-9.2	0.24
Fasting glucose (mg/dL)	96	90-106	100.53	88.25-115	96	88-108.5	0.39
TSH (mU/L)	1.13	0.88-1.77	1.52	0.76-2.02	1.13	0.84-1.83	0.4
Total cholesterol (mg/dL)	183.5	163.75-216.25	195	156-216	185	160-216	0.75
Triglyceride (mg/dL)	163.5	128.5-207.75	166	120.75-203	165	123.75-204.25	0.89
HDL (mg/dL)	44	38.15-51.32	40.5	35-45.65	42	36-48	0.054
LDL (mg/dL)	97.5	80.22-135	112	90.05-131.12	103	84-132	0.39
WBC (k/mm^3)	9.35	7.7-10.67	8.48	7.22-10.24	8.91	7.57-10.5	0.1
Hb (g/dL)	13.4	12.4-14.6	13.6	12.45-14.72	13.6	12.4-14.65	0.93
Platelet	276	225-298	264	215.75-313.5	272	220-302.5	0.64
HbA1c	5.42	5.1-5.8	5.89	5.43-6.15	5.6	5.18-6	0.001
LVEF (%)	60	55-60	50	40-60	60	50-60	<0.001

IQR: Interquartile range; Na: Sodium; K: Potassium; Ca: Calcium; TSH: Thyroid stimulating hormone; HDL: High density lipoprotein; LDL: Low density lipoprotein; WBC: White blood cell; Hb: Hemoglobin; HbA1c: Hemoglobin A1c; LVEF: Left ventricular ejection fraction.

Table 3
Medications used by patients

	Coronary lesion <70% (n=71)		Coronary lesion >70% (n=54)		Total (n=125)		
	n	%	n	%	n	%	*p*
Beta-blockers	17	23	18	33	35	28	0.31
ACEi	16	22	18	33	34	27	0.22
ARBs	7	9	5	9	12	9	1
Dhp CCBs	8	11	13	24	21	16	0.08
Non-Dhp CCBs	7	9	4	7	11	8	0.75
Antiplatelet	21	29	20	37	51	40	0.44
Anticoagulant	6	8	2	3	8	6	0.46
Statin	15	21	17	31	32	25	0.21

ACEi: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; Dhp CCB: Dihydropyridine calcium channel blockers.

There was no difference between the groups in terms of drug use. The laboratory findings of the patients and the drugs they used are summarized in Tables 2 and 3.

The median HbA1c value in Group 2 was statistically higher than in Group 1 [5.89 (5.43-6.15) *vs.* 5.42 (5.1-5.8), p=0.001]. In the ROC analysis, a HbA1c >5.66 had 64% sensitivity

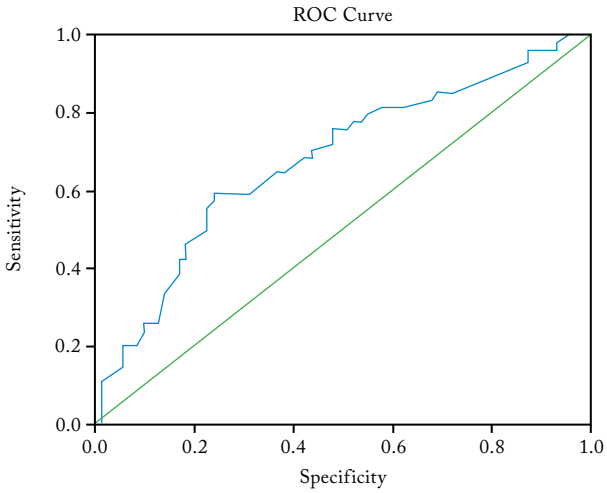

Figure 1. The sensitivity and specificity of HbA1c associated with coronary artery lesion severity in the ROC curve.
ROC: Receiver operating characteristic; HbA1c: Hemoglobin A1c.

and 63% specificity (area under the curve: 0.68, 95% confidence interval: 0.585-0.776, p=0.001) for determining the coronary artery lesion severity (Figure 1).

DISCUSSION

This is a rare study in the literature that aimed to determine the correlation between coronary artery lesion severity determined by coronary CTA and HbA1c value in nondiabetic patients. In our study, the median HbA1c levels were significantly higher in the patient group with significant coronary artery stenosis compared to the group with nonsignificant coronary artery stenosis (p<0.001), and there was a strong correlation between coronary artery lesion severity and the HbA1c value in nondiabetic patients with CCS.

One of the confounding factors affecting HbA1c is the hemoglobin value, as it changes HbA1c. A low hemoglobin value may lower the HbA1c level. Therefore, low hemoglobin status may show an inaccurate relationship between CAD severity and low HbA1c levels.[9] One of the advantages of our study is that the median hemoglobin values were within normal limits in both groups.

Garg et al.,[10] Ayhan et al.,[11] and Kis and Guzel[12] found the cut-off values of HbA1c as 5.7, 6.52, and 5.5, respectively, and concluded that it was an independent predictor of the severity of CAD in nondiabetic patients. In our study, the HbA1c cut-off value was determined as 5.66 as a predictor of a severe coronary artery lesion in coronary CTA.

Hemoglobin A1c is a parameter that is used in the diagnosis and follow-up of DM and quantitatively shows the three-month glycemic control. It is possible to establish a relationship between HbA1c and coronary atherosclerosis, considering that exposure to high blood sugar causes vascular complications. Unregulated blood sugar induces oxidative stress, and the developing glycation end products and lipid peroxidation products initiate endothelial damage. As a result, an inflammatory process develops, and atherogenesis becomes active.[13] Hemoglobin A1c is also an advanced glycation end product.

In a study by Haring et al.[14] in 1798 nondiabetic patients, it was shown that the carotid intima-media diameter increased by 0.02 mm for each 1% increase in HbA1c. The study of Kayalı and Ozder[15] hypothesized that HbA1c predicts CAD in nondiabetic patients. In the study, 247 patients were recruited and classified according to the coronary arteries lesion severity, and a close relationship was found between HbA1c and coronary stenosis. When the recent prospective studies were examined, it was observed that although some claimed the opposite between HbA1c and CAD, most of them contributed to the literature. It has been shown that each percentage increase in HbA1c in nondiabetic patients increases the risk of CAD 1.2 times.[16] In a study that included 93 patients investigating the relationship between the severity of coronary atherosclerosis and HbA1c, HbA1c values were found to be higher in the group with severe atherosclerosis.[17] In the study of Dutta et al.,[18] it was concluded that as the HbA1c level increased, the number of affected vessels in the coronary arteries also significantly increased.

Ashraf et al.[19] investigated whether HbA1c was an independent predictor of CAD in their study of 382 patients with suspected coronary ischemia without a known history of DM. However, while age and sex were statistically significantly higher at first, among the cardiovascular risk factors (for example, sex, hypertension, dyslipidemia, and smoking), no statistically significant difference was observed after additional analysis. We can believe that these risk factors that may cause CAD may have affected the outcome of the current study. However, a significant

difference was found between the two groups only in terms of hypertension, which is one of the etiological factors that may cause coronary atherosclerosis. In this study, LVEF was found to be lower in the group with more severe coronary lesions. This result was thought to be due to the negative effect of coronary ischemia on left ventricular systolic function. In our study, the hypertension rate was higher and the median LVEF value was lower in the group with higher coronary lesion severity.

There are several limitations to this study. First, the HbA1c values of the patients were calculated when the patients were admitted to the hospital. The HbA1c value is based on a single measurement; thus, it may underestimate any relationship between HbA1c and coronary artery lesion severity. Second, coronary CTA calcium score was not included in the analysis as the selected patient population differed according to whether severe lesions were detected. Although the study population was relatively small, the patient group was found to be sufficient in the power analysis performed before the study. However, studies involving more patients are needed, and we believe that our study may be a pioneer for further studies on this subject. Since we do not have long-term follow-up results, we do not know the prognostic value of HbA1c in the long-term follow-up of patients with CCS.

In conclusion, in nondiabetic patients with CCS, HbA1c, which shows the long-term glycemic index, is associated with severe coronary artery lesions detected in CTA. Controlling the HbA1c values of patients while planning diagnostic coronary CTA may be a guide in patients with suspected nondiabetic CAD.

Ethics Committee Approval: The study protocol was approved by the Bakırçay University Medicine Faculty Ethics Committee (date: 03.08.2022, no: 684). 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: Idea/concept, design, control/supervision, critical review: M.K., Data collection and/or processing, analysis and/or interpretation, references and fundings, materials: F.S.Y.; Literature review, writing the article: F.S.Y., M.K.

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Role of the uric acid/albumin ratio in predicting mortality of patients who underwent transcatheter aortic valve implantation

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ABSTRACT

Objectives: The aim of this study was to investigate whether baseline uric acid/albumin ratio (UAR) was a predictor for mortality in patients who underwent transcatheter aortic valve implantation (TAVI) due to severe aortic stenosis.

Patients and methods: The retrospective study included 240 patients (121 females, 119 males; mean age 77.5±7.6 years; range, 52 to 95 years) who underwent TAVI between January 2015 and January 2020 in two centers. Patient characteristics were compared between two groups according to mortality during follow-up (the mortality group and the survival group). The value of the UAR in predicting mortality was evaluated with receiver operating characteristic curve analysis. Predictors of mortality after TAVI were investigated with Cox regression analysis.

Results: In-hospital mortality developed in 16 (6.7%) patients, and postdischarge all-cause mortality was observed in 41 (17.1%). The two-year mortality rate was determined to be 15%. The rate of systolic heart failure, systolic pulmonary artery pressure, and UAR were found to be significantly higher in the mortality group (p=0.007, p=0.036, and p<0.001, respectively). The diagnostic power of UAR in predicting mortality was poor (the area under the curve=0.671, confidence interval [CI]: 0.589-0.753, p<0.001). Independent predictors of mortality after TAVI were UAR >2.03 (hazard ratio=2.958, CI: 1.623-5.393, p<0.001) and platelet count (hazard ratio=0.996, CI: 0.992-1.000, p=0.05).

Conclusion: Uric acid/albumin ratio was found to be an independent predictor for short-and long-term all-cause mortality in patients who underwent TAVI.

Keywords: Albumin, mortality, severe aortic stenosis, transcatheter aortic valve implantation, uric acid.

Transcatheter aortic valve implantation (TAVI) is an alternative treatment method in patients with severe aortic stenosis, particularly those at high risk for surgical aortic valve replacement. In addition to markers such as the logistic EuroSCORE (European system for cardiac operative risk evaluation), the New York Heart Association functional classification, the Society of Thoracic Surgeons Predicted Risk of Mortality algorithm, and postoperative acute renal failure, baseline albumin levels has also been shown to be a predictor for mortality after TAVI.[1-4]

Albumin not only provides intravascular oncotic pressure and functions as a hormone, drug, and free fatty acid transporter but also plays an important role as an anti-inflammatory and antiapoptotic factor and provides protection against oxidative stress.[5-7] Serum levels of albumin may be reduced due to reduced synthesis in the liver, malnutrition, increased catabolism, reduced absorption from the gastrointestinal system, and inflammation-related capillary leakage.[8] Low levels of serum albumin are associated with coronary artery disease, acute renal failure, and all-cause mortality.[9,10]

Uric acid is the end-product of the purine metabolism. Two-thirds of uric acid is excreted by the kidneys, while the remaining one-third is excreted by intestinal uricolysis.[11,12] An increased level of uric acid is associated with endothelial dysfunction, increased inflammation and oxidative stress, and activation of the renin angiotensin aldosterone system.[13,14]

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An increased level of uric acid is also an independent predictor of cardiovascular disease, aortic dilatation, hypertension, cardiovascular event, kidney failure, and all-cause mortality.[15-18]

A previous study showed that uric acid/albumin ratio (UAR) was shown to be associated with short-term mortality in acute renal failure patients.[19] Similarly, Wang et al.[20] found that UAR was an independent risk factor for postoperative long-term mortality in type A aortic dissection patients.

To the best of our knowledge, no study has been conducted to investigate whether UAR is an independent predictor for mortality following TAVI. Therefore, this study aimed to evaluate the prognostic value of UAR for mortality in TAVI patients.

PATIENTS AND METHODS

The retrospective study was conducted at two centers with 240 patients (121 females, 119 males; mean age 77.5±7.6 years; range, 52 to 95 years) who underwent TAVI between January 2015 and January 2020. The exclusion criteria were defined as follows: *(i)* having a comorbid congenital disease, *(ii)* a history of malignancy, *(iii)* a history of metabolic or hormonal disease other than diabetes or thyroid disease, *(iv)* a history of liver disease other than Grade 1 or 2 hepatic steatosis or a history of chronic gastrointestinal disease, *(v)* a diagnosis of sepsis, decompensated heart failure, or cardiogenic shock, *(vi)* having Grade ≥4 renal failure (creatine clearance <30 mL/min/1.73m^2) before the procedure, and *(vii)* a history of gout. The patients were evaluated in two groups according to mortality during follow-up (the mortality group and the survival group).

The demographic, clinical, laboratory, and procedural characteristics of the patients were recorded. The laboratory results were obtained from fasting blood samples taken between 9:00 am and 12:00 am before the procedure. The follow-up periods and mortality status of the patients were obtained from the national healthcare system. All patients underwent two-dimensional echocardiography within 24 h before the procedure. Left ventricular ejection fraction was calculated using the modified Simpson method. Patients with a fasting blood glucose >126 mg/dL measured on two separate occasions during hospitalization and those receiving antidiabetic treatment were accepted as diabetic. Patients with brachial blood pressure >140/90 mmHg measured on two separate occasions during hospitalization and those receiving anti-hypertensive treatment were accepted as hypertensive. A left ventricular ejection fraction <40% was accepted as systolic heart failure. The glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula.[21]

Statistical analysis

Statistical analyses were performed using the MedCalc version 20.014 software (MedCalc Software Ltd., Ostend, Belgium). Continuous variables with normal distribution according to the Kolmogorov-Smirnov test were expressed as mean ± standard deviation, and those not showing normal distribution were presented as median (interquartile range [IQR]). Categorical variables were expressed as number (n) and percentage (%). Comparisons of the variables between the two groups were performed with the paired samples t-test, Mann-Whitney U test, and the chi-square test. The receiver operating characteristic curve analysis was used to determine the diagnostic power of UAR and albumin level and the cutoff value of UAR for the optimal sensitivity and specificity in predicting mortality. The Kaplan-Meier survival analysis and the log-rank test were used to determine and compare the survival periods of the two groups separated by the cutoff UAR value. To determine independent predictors of mortality after TAVI, univariate and multivariate Cox regression analyses were used. Parameters with statistical significance in the univariate analysis were included in the subsequent multivariate analysis. A p value <0.05 was accepted as statistically significant.

RESULTS

The median follow-up period was 36 months (IQR: 18.75-47 months). The median logistic EuroSCORE was 28.25 (IQR: 5-86). A bicuspid aorta was determined in 11 (4.6%) patients.

Permanent pacemaker implantation due to new-onset atrioventricular complete block after the TAVI was performed in 25 (10.4%) patients. The rate of baseline right bundle branch block was significantly higher among the patients who developed new-onset atrioventricular complete block than among the patients who did not (34.8% *vs.* 12.9%, p=0.01). Valve-in-valve implantation due to severe aortic regurgitation was performed in eight (3.3%) patients.

Table 1
Demographic and clinic characteristics of the patients

	Survival group (n=183)					Mortality group (n=57)					
Variables	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			77.9±7.6					77.6±7.8			0.797
Sex											
Male	92	50.3				27	47.4				0.702
Body mass index (kg/m^2)			26.8±4.7					26.3±3.2			0.470
Diabetes	71	38.8				15	26.3				0.086
Coronary artery disease	74	40.4				25	43.9				0.647
Hypertension	132	72.1				42	73.7				0.819
Systolic heart failure	46	25.1				25	43.9				0.007
Low-gradient aortic stenosis	37	20.2				15	26.3				0.329
Stroke	10	5.5				3	5.3				0.953
Hypoalbuminemia (<3.5 g/dL)	52	28.4				36	63.2				<0.001
COPD	30	16.4				12	21.1				0.419
Cancer	5	2.7				5	8.8				0.060
Atrial fibrillation	46	25.1				20	35.1				0.142
RBBB	29	15.8				7	12.3				0.510
Bicuspid aortic valve	10	5.5				1	1.8				0.242
Beta-blocker	114	62.3				33	57.9				0.552
ACE inh/ARB	139	76				36	63.2				0.058
Diuretic	116	63.4				30	52.6				0.146
Mineralocorticoid receptor antagonist	53	29.0				16	28.1				0.897
Valve type											0.357
SAPIEN XT	29	15.8				12	21.1				
ACURATE neo	48	26.2				9	15.8				
St. Jude Medical Portico	53	29.0				16	28.1				
CoreValve Evolut R	53	29.0				20	35.1				
Log. EuroSCORE (%)				28.00	5.00-86.00				30.08	9.00-85.90	0.095

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; RBBB: Right bundle branch block; ACE inh: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; Log. EuroSCORE: Logistic European system for cardiac operative risk evaluation.

Table 2
The laboratory and echocardiographic characteristics of the patients

Variables	Survival group (n=183)			Mortality group (n=57)			*p*
	Mean±SD	Median	25th-75th percentile	Mean±SD	Median	25th-75th percentile	
Hemoglobin (g/dL)	11.5±1.7			11.2±1.8			0.243
CrCl (mL/min)		62.27	43.84-76.70		58.76	40.23-77.91	0.546
Sodium (mEq/L)	137.2±3.9			137.6±3.6			0.447
Potassium (mmol/L)	4.6±3.0			4.3±0.7			0.374
White blood cell ($\times10^9$/L)	7.9±2.8			7.6±2.3			0.548
hs-CRP (mg/L)		2.86	0.65-4.10		3.11	1.05-5.96	0.145
ALT (IU/L)	23.1±36.8			20.7±29.1			0.653
AST (IU/L)	27.6±28.5			26.7±30.9			0.837
TSH (mIU/L)		1.37	0.90-2.30		1.45	0.75-3.27	0.736
Platelet ($\times10^3$/L)	235.0±76.4			212.4±72.4			0.050
Triglyceride (mg/dL)	136.3±83.7			128.9±56.3			0.533
LDL (mg/dL)	108.0±38.0			108.4±38.3			0.938
BNP (pg/mL)		1481	636- 4347		2336	952-3942	0.125
Albumin (g/dL)	3.7±0.5			3.4±0.6			<0.001
Uric acid (mg/dL)	7.1±2.1			7.8±2.0			0.054
UAR	2.0±0.6			2.3±0.7			<0.001
Pre-op (LVEF %)	46.0±12.0			41.9±13.1			0.027
PASP (mmHg)	49.8±13.4			54.2±15.2			0.036
AVA (cm^2)	0.7±0.1			0.7±0.1			0.579
TAPSE (mm)	20.6±2.7			20.4±2.8			0.541

SD: Standard deviation; CrCI: Creatinine Clearance; hs-CRP: High sensitivity c-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TSH: Thyroid-stimulating hormone; LDL: Low-density lipoprotein; BNP: Brain natriuretic peptide; UAR: Uric acid/albumin ratio; LVEF: Left ventricular ejection fraction; PASP: Pulmonary artery systolic pressure; AVA: Aortic valve area; TAPSE: Tricuspid annular plane systolic excursion.

Following TAVI, acute renal failure was determined in 28 (11.7%) patients, peripheral vascular damage (e.g., dissection, hematoma) in 32 (13.3%), ischemic stroke in six (2.5%), myocardial infarction in 10 (4.2%), and ascending aorta dissection in two (0.8%). In-hospital mortality occurred in 16 (6.7%) patients, whereas postdischarge all-cause mortality occurred in 41 (17.1%). Of 16 in-hospital deceased patients, two patients died due to stroke, two patients due to ascending aorta dissection, three patients due to myocardial infarction, three patients due to peripheral vascular damage, one patient due to nosocomial pneumonia, three patients due to decompensated heart failure/cardiogenic shock, and two patients due to an unknown cause. The two-year mortality rate was determined to be 15% (n=36).

When the demographic and clinical characteristics of the patients were compared, the rate of systolic heart failure was found to be higher in the mortality group compared to the survival group (43.9% *vs.* 25.1%, p=0.007). The demographic and clinical characteristics of the patients are shown in Table 1.

When the laboratory and echocardiographic data of the patients were compared, the albumin level was significantly lower and the UAR was significantly higher in the mortality group (p<0.001 and p=0.001, respectively). The laboratory and echocardiographic data of the patients are shown in Table 2.

The area under the curve (AUC), evaluated for determining the diagnostic power of UAR in

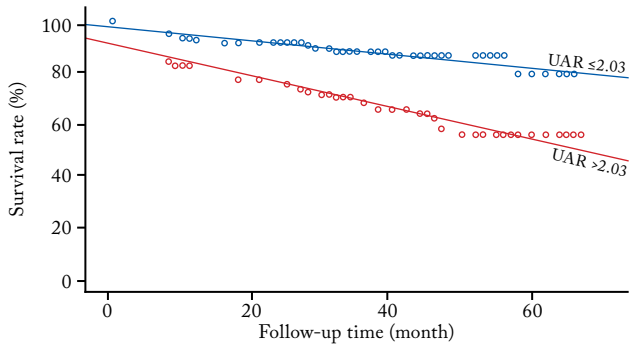

Figure 1. Kaplan-Meier analysis comparing the survival periods in patients above and below the cut off value of UAR.
UAR: Uric acid/albumin ratio.

Table 3
Cox regression analysis for identifying predictors of mortality following TAVI

Variables	HR	95% CI	*p*
Univariate analysis			
SHF	1.956	1.159-3.301	**0.012**
Platelet count	0.996	0.992-1.000	**0.039**
UAR >2.03	3.139	1.741-5.662	**<0.001**
PASP	1.016	0.998-1.035	0.086
Multivariate analysis			
SHF	1.457	0.850-2.497	0.171
Platelet count	0.996	0.992-1.000	**0.05**
UAR >2.03	2.958	1.623-5.393	**<0.001**

TAVI: Transcatheter aortic valve implantation; HR: Hazard ratio; CI: Confidence interval; SHF: Ssystolic heart failure; UAR: Uric acid/albumin ratio; PASP: Pulmonary artery systolic pressure.

predicting mortality, was 0.671 (confidence interval [CI]: 0.589-0.753, p<0.001). No significant difference was found between the AUC of albumin and the AUC of UAR (0.675 *vs.* 0.671, p=0.93). A UAR value >2.03 had 70.2% sensitivity and 60.1% specificity in predicting all-cause mortality.

In the Kaplan-Meier survival analysis, the survival period was significantly shorter in the group with a UAR >2.03 (46.9 months *vs.* 58.6 months, p<0.001, Figure 1).

In the univariate Cox regression analysis, systolic heart failure, platelet count, and a UAR >2.03 were found to be associated with mortality after TAVI. In the multivariate regression analysis, UAR >2.03 (hazard ratio=2.958, CI: 1.623-5.393, p<0.001) and platelet count (hazard ratio=0.996, CI: 0.992-1.000, p=0.05) remained as independent predictors for mortality after TAVI (Table 3).

DISCUSSION

This study investigated the prognostic value of UAR for mortality in TAVI patients. The results showed the in-hospital mortality rate to be 6.7% and the postdischarge all-cause mortality to be 17.1%. Although the predictive power of UAR for mortality was poor in the receiver operating characteristic analysis, a UAR above the cutoff value of 2.03 was an independent predictor of increased risk of mortality following TAVI. A decreased platelet count was also an independent predictor of mortality.

In a study in 2016, Gaede et al.[22] evaluated the results of 15,050 patients who had undergone TAVI and reported an in-hospital mortality rate of 2.6% and a permanent pacemaker implantation rate of 11.4%. Additionally, in this study, a cerebrovascular event was observed in 2.2%, vascular complications in 7.1%, myocardial infarction in 0.2%, and acute renal damage in 3%. Compared to the results of the current study, the lower rates of vascular complications, in-hospital mortality, and acute renal damage can be considered to be due to a difference in the experience of the operators and different study populations. In a 2013 study by Finkelstein et al.,[23] the outcomes of 300 TAVI patients were reported and in-hospital mortality, stroke, minor vascular complication, and permanent peacemaker implantation rates were 2.3%, 1.6%, 10.7%, and 22%, respectively. Although the in-hospital mortality rate was low compared to the rate in the current study, the high rate of permanent pacemaker implantation could have been due to the use of older generation bioprosthetic valves. Gleason et al.[3] evaluated patients implanted with a self-expandable valve, and found the five-year mortality rate after TAVI to be 55.3%. The significantly higher mortality could be attributed to the difference in the study populations and the shorter follow-up period in that study.

The current study results showed a low platelet count to be an independent predictor of mortality following TAVI. In parallel to the current study results, Kalińczuk et al.[24] also reported that a reduced platelet count after TAVI was associated with increased mortality. In another study, the development of thrombocytopenia after TAVI was found to be a predictor of 30-day

mortality, and platelet count before the TAVI was the only predictor of thrombocytopenia.[25] Similarly, it can be considered that a lower thrombocyte count in the current study may have increased the risk of thrombocytopenia development after TAVI. However, there is a need for further studies on this subject.

In a previous meta-analysis, the baseline albumin level was found to be an independent predictor of 30-day and one-year mortality after TAVI.[4] This finding is compatible with the finding of the current study that the albumin level was significantly lower in the mortality group. The mounting evidence indicating that low albumin level is related to endothelial dysfunction, subclinical systemic inflammation, and renal and liver dysfunction could explain the increased mortality in TAVI patients. Moreover, a decreased albumin level causes decreased intravascular osmotic colloidal pressure, which may accelerate the development of acute renal damage, pulmonary edema, or decompensated heart failure in TAVI patients.[5,26,27]

In a study by Sokmen et al.,[1] although the baseline uric acid level was significantly higher in patients who deceased after TAVI, it was not found to be an independent predictor of mortality. It has been previously stated that a high uric acid level is associated with increased inflammation, renin-angiotensin aldosterone activation, endothelial dysfunction, and aorta dilatation.[13,14,28]

To minimize the effect of the confounding factors on uric acid and albumin levels, these two markers were combined in the current study. Evidence related to the prognostic importance of uric acid and albumin levels may explain why the ratio of these two markers is a predictor of mortality following TAVI.

This study has several limitations. This study was retrospective in design, was conducted in only two centers, and the number of patients included was relatively limited. The scores other than the logistic EuroSCORE were not evaluated. Only four types of bioprosthetic valves were preferred so there was no experience with other bioprosthetic valves (e.g., Myval). When evaluating UAR and platelet count, only preprocedural blood results were used. Therefore, the effects of change in UAR and platelet count could not be investigated.

In conclusion, UAR, an easy-to-obtain and practical marker, was found to be an independent predictor of mortality after TAVI. Therefore, it would be appropriate to investigate the value of this marker with more evidence-based research methods to determine the risk of death in TAVI patients.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital Ethics Committee (date: 02.11.2022, no: 2011-KAEK-25 2022/11-15). 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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Comparison of flexible and rigid annuloplasty rings in isolated mitral regurgitation

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ABSTRACT

Objectives: The aim of this study was to examine the early and midterm results of various annuloplasty rings in terms of residual mitral regurgitation (MR) in patients undergoing mitral valve repair.

Patients and methods: In the retrospective study, 298 patients (157 males, 141 females; mean age: 58.8±14.3 years; range, 16 to 82 years) underwent repair between September 2009 and April 2012. Two hundred eleven were assigned to the flexible ring group (Group 1), whereas 87 were included in the rigid ring group (Group 2). Mitral pathologies were divided into three subgroups: ischemic, degenerative, and rheumatic.

Results: The causes of mitral pathology were ischemic in 36.2%, degenerative in 54.4%, and rheumatic in 9.4%. Concomitant surgical procedures were present in 87%. The follow-up period ranged from 2 days to 33 months, with a mean of 15.8±7.5 months. The 30-day mortality rate was 9.2% and 10.4% in Groups 1 and 2, respectively. There was a high rate of successful repair in the rigid group with 88.5% and acceptable rate of repair in the flexible group with 72%. Mitral regurgitation was significantly reduced after intervention regardless of the ring type ($p<0.01$). Significant improvement in NYHA class was observed in both groups. Recurrent regurgitation was detected in 27.9% of patients in Group 1 and 11.5% in Group 2. Recurrence occurred within three to nine months following the surgery. Reoperation rates for residual MR were 3.3% (n=7) vs. 1.1% (n=1) in Groups 1 and 2, respectively ($p=0.293$).

Conclusion: Saddle-shaped rings provide a mechanical benefit through a low and uniform force distribution and improve repair durability compared to flat rings. As a result, the rigid ring had a significant advantage, particularly in degenerative and rheumatic subgroups, but there was a loss of superiority in late ischemic MR due to left ventricle remodeling.

Keywords: Mitral valve, mitral valve annuloplasty, mitral valve insufficiency.

Annuloplasty is an essential component in mitral valve (MV) repair, which is currently the gold standard treatment for symptomatic severe mitral regurgitation (MR).[1] The choice of ring for MV repair is left to the surgeon's preferences, and there are no specific guidelines for regulation. In time, MV repair has become the preferred operative technique with the increased experience of surgeons. The success of repair may vary by ring type, annuloplasty technique, and left ventricle (LV) remodeling.[2,3] The use of flexible rings is justified for degenerative MV disease, whereas saddle shaped-rigid ring is elected in patients with ischemic or myxomatous MR.[4,5] Hence, we compared the early and midterm results of MV repair with flexible and rigid rings in three subgroups.

PATIENTS AND METHODS

In the retrospective study, 298 patients (157 males, 141 females; mean age: 58.8±14.3 years; range, 16 to 82 years) underwent MV repair due to isolated MR at the Koşuyolu High Specialization Education and Research Hospital between September 2009 and April 2012. The causes of mitral pathology were ischemic in 36.2%, degenerative in 54.4%, and rheumatic in 9.4%. Follow-up data regarding echocardiographic parameters and complications were determined at the patient's last visit or by telephone interview. The mean additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) was calculated in both groups. Demographic data, comorbidities, degree of MR, and LV function were similar, except for New York Heart Association

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(NYHA)>2 (p=0.031), EuroSCORE (p=0.001), and hypertension (p=0.026, Table 1). Overall, 76.5% of patients defined NYHA class III/IV symptoms. Primary endpoints involved recurrent MV regurgitation, NYHA, and LV positive remodeling.

Surgical technique

Patients who had concomittant mitral stenosis and patients without ring annuloplasty were excluded. Depending on the type of ring used in annuloplasty, we divided patients into 2 groups: flexible ring (St. Jude Medical® Flexible Tailor™ Annuloplasty Ring, Inc. St. Paul, MN,USA), group 1; rigid ring (St. Jude Medical® Rigid Saddle Ring with EZ Suture™ Cuff, Inc. St. Paul, MN,USA), group 2. Depending on the valve pathology, each group was divided into three subgroups: ischemic, degenerative, and rheumatic. The flexible ring (n=211, 70.8%) was mainly selected for patients with a degenerative base, and the rigid ring was chosen in ischemic or functional MR for down-sizing. However, ring choice was determined by the availability or the surgeon's discretion during that period. Concomitant procedures were tricuspid valve reconstruction, coronary artery bypass grafting, aortic valve replacement, ascending aortic interposition, and atrial septal defect closure, as can be seen in Table 2.

Echocardiographic data

The endpoints of interest include early and late mortality, alterations in NYHA, LV ejection fraction (EF), left atrial (LA) size, LV diameters, freedom from reoperation, and residual MR. Mitral regurgitation was reported as none, mild, moderate, or severe, based on the American Society of Echocardiography guidelines.[6] All MR grades were site-determined. Indications for surgery were defined as Class I symptomatic (severe MR with symptoms), Class I asymptomatic (severe

Table 1
Preoperative data

	Flexible (Group 1) (n=211)			Rigid (Group 2) (n=87)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			59.0±14.6			58.3±13.7	0.716
Female	95	45		46	52.9		0.217
Coronary artery disease	103	48.3		38	43.7		0.402
Renal failure	25	11.8		11	12.6		0.848
Obstructive lung disease	52	24.6		25	28.7		0.464
Diabetes mellitus	47	22.3		16	18.4		0.456
Hypertension	82	38.9		22	25.3		0.026*
Atrial fibrillation	56	26.5		29	33.3		0.401
MR etiology							
Ischemic	74	35.1		34	39.1		
Degenerative	121	57.3		41	47.1		
Rheumatic	16	7.6		12	13.8		
Logistic EuroSCORE I			3.7±1.2			4.9±2.0	0.001*
NYHA Class III-IV	172	81.5		56	64.3		0.031*
Echocardiographic data							>0.05
LA (mm)			45.0±7.9			46.3±8.3	
LVEDD (mm)			57.2±7.4			58.5±7.4	
LVESD (mm)			41.9±8.7			42.9±8.9	
LVEF, %			47.8±14.0			48.2±13.7	
MR moderate	24	11.4		7	8		
MR severe	187	88.6		80	92		

SD: Standard deviation; MR: Mitral regurgitation; EuroSCORE: European system for cardiac operative risk evaluation; NYHA: New York Heart Association; LA: Left atrium; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; LVEF: Left ventricular ejection fraction.

Table 2
Surgical data

	Flexible (Group 1) (n=211)					Rigid (Group 2) (n=87)				
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max
Mitral valve repair										
P2 plication	140	66.4				10	11.5			
Triangular resection	0	0				3	3.4			
Quadrangular resection	3	1.4				3	3.4			
Alfieri stitch	5	2.4				1	1.1			
Chordal transfer	4	1.9				0	0			
Neochordae implantation	20	9.5				5	5.7			
Concomitant procedures										
Tricuspid reconstruction	64	30.3				31	35.6			
CABG	83	39.3				32	36.8			
Aortic reconstruction/AVR	15	5.7				6	6.8			
ASD closure	7	3.3				1	1.1			
Bentall	2	0.9				1	1.1			
Ascending aortic replacement	5	2.4				1	1.1			
X-clamp time (min)			72.5±30.1		18-182			79.2±27.7		31-171
CPB time (min)			115.5±47.9		44-471			120.4±40.1		52-240
Length of ICU (d)			5.45±6.94	4	1-58			4.9±6.1	8	1-32
Length of hospital stay (d)			8.98±4.17	3	3-32			7.4±2.7	6	5-20

SD: Standard deviation; CABG: Coronary artery bypass graft; AVR: Aortic valve replacement; ASD: Atrial septal defect; CPB: Cardiopulmonary bypass; ICU: Intensive care unit.

MR and LVEF of 30 to 60% or a LV end-systolic diameter [LVESD] ≥40 mm), Class IIa asymptomatic without triggers (severe MR and LVEF >60%, LVESD <40 mm, and either atrial fibrillation or pulmonary artery systolic pressure >50 mmHg).[1] According to the postoperative echocardiographic evaluation, those with MR ≥2 were classified as recurrent MR. Comparative echocardiograms for each group were performed one month after discharge and at least six months following surgery.

Statistical analysis

Data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as absolute values and frequencies (%), and continuous variables are presented as the mean and standard deviation. Comparisons between the groups were carried out using the paired sample t-test or the Wilcoxon test for continuous variables, and Fisher exact test, the chi-square test, or the McNemar test were utilized for categorical variables. Univariate and multivariate Cox proportional hazard functions were used to determine predictors for recurrent MR. Freedom from recurrence and reoperation analysis are presented as Kaplan-Meier curves. A two-tailed *p*-value of <0.05 was considered statistically significant.

RESULTS

Eleven (5.2%) of the cases in Group 1 and three (3.4%) in Group 2 had a prior cardiac operation. Obstructive lung disease (25.8%) and hypertension (34.9%) were the most frequent comorbid conditions. Overall, follow-up period ranged from 2 days to 33 months, with a mean of 15.8±7.5 months. Surgical data can be viewed in Table 2. The mean ring size was 29.4±1.5 mm (median: 29 mm) in Group 1 and 31.0±1.8 mm (median; 32 mm) in Group 2. The mean (range) aortic cross-clamp and cardiopulmonary bypass (CPB) times were 72.5±30 (range, 18-182) min and 115.5±47.9 (range, 44-471) min for Group 1 and 79.1±27.6 (range, 31-171) min and 120.4±40.1 (range, 52-240) min for Group 2, respectively. There were no preoperative differences between groups in terms of echocardiographic parameters (p>0.05). Intraoperative transesophageal echocardiogram (TEE) showed adequacy of

Table 3
Postoperative complications

	Flexible (Group 1) (n=211)		Rigid (Group 2) (n=87)		
	n	%	n	%	*p*
Inotropic support	112	53.1	44	50.6	0.694
Renal failure	30	14.2	13	14.9	0.872
Arrhythmia	33	15.6	22	25.3	0.186
Respiratory failure	40	19.0	8	9.2	0.037*
Infection	16	7.6	7	8.0	0.892
Neurological	8	3.8	1	1.1	0.226
Surgical revision	14	6.6	4	4.6	0.503
Reoperation	7	3.3	1	1.1	0.293

surgical repair (MR<moderate) in all patients. The assessment of repaired MV by post-CPB TEE comprised measure of trans-mitral gradient, leaflet coaptation surface, and LV function. Posterior leaflet segment 2 plication of posterior leaflet and neochordae implantation were more common, and concomitant approaches were comparable in both groups. Cross-clamp and CPB times were shorter in Group 2. There was a higher rate of successful repair in Group 2 with 88.5% compared to the acceptable repair rate of Group 1 with 72%.

Postoperative complications were as follows: renal failure in 14.4%, arrhythmia in 18.5%, respiratory failure in 16.1%, infection in 7.7%, and neurological incident in 3%. There was no significant difference between groups in terms of complications, except for respiratory failure, which was higher in Group 1 (p=0.037, Table 3). Atrial fibrillation and ventricular extrasystole were observed and treated medically. One patient in Group 2 needed permanent pace maker following radiofrequency ablation. Surgical revision was needed in 14 patients in Group 1 and four patients in Group 2 due to bleeding, cardiac tamponade, and pleural decortication.

Thirty-day mortality rate was 10.4% in Group 1, whereas it was 9.2% in Group 2. Causes of death were cardiac in 28 patients, multiorgan failure in 16, and cerebrovascular accident in two. Deceased patients had higher EuroSCORE values (p=0.001). Follow-up was available in 294 (98.6%) patients; furthermore, late echocardiogram was applied in 76.4% and 92.5% for group 1 and 2, respectively. The mean time of follow-up/echocardiographic control was 11.1±7.0 months (median: 12; range, 2 days to 25 months) in Group 1 and 9.8±6.0 months (median: 9; range, 3 days to 22 months) in Group 2. The late mortality rate was 6.6% (n=14) in Group 1 and 3.4% (n=3) in Group 2.

The decrease in LA and LVEDD was more significant in ischemic (p=0.03, p=0.029) and

Table 4
Predictors of recurrent MR

Univariate analysis		*p*
Echocardiographic		
LVEDD		0.001
LVESD		0.001
LVEF		0.144
Mitral regurgitation		
Moderate		0.060
Severe		
Ring type		
Flexible		0.002
Rigid		
Ring no		0.209
Concomitant procedures		0.118
Multivariate analysis	**Odds ratio**	***p***
Preoperative MR	3.698	0.038
Preoperative LVEDD	1.036	0.001

MR: Mitral regurgitation; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; LVEF: Ejection fraction.

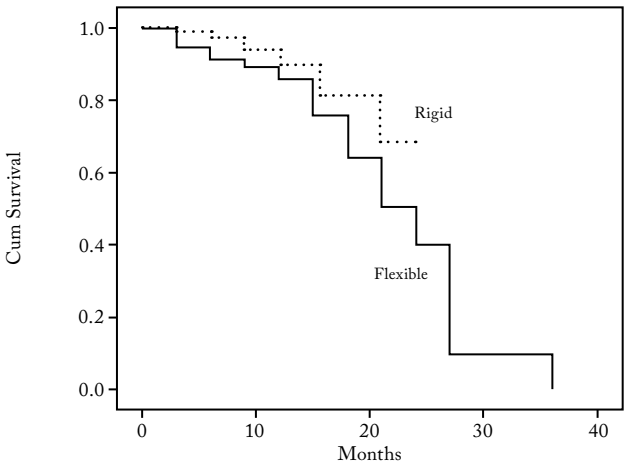

Figure 1. Recurrence free survival.

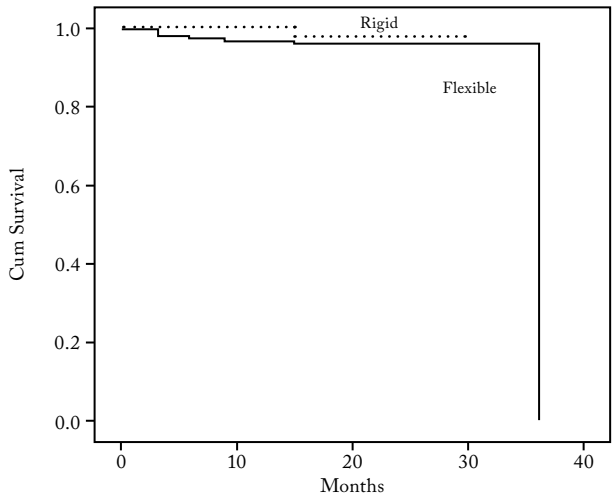

Figure 2. Reoperation free survival.

degenerative (p=0.05, p=0.014) subgroups of rigid rings. Nevertheless, systolic function did not improve and did not differ between ring types (p>0.05). There is no statistical difference in the reduction of LA (p=0.184), LVEDD (p=0.488), and EF (p=0.777) between rings in the rheumatic subgroup.

On-table TEE was performed to all patients in both groups. Mitral regurgitation was strongly reduced after intervention regardless of the ring type (p<0.01). A gradient >5 mmHg was not detected following valve repair. For the purpose of tailored selection of annuloplasty ring, we subdivided each group into ischemic, degenerative, and rheumatic pathology and examined the effect of ring type on valve pathologies. Improvement in MR with rigid ring was significantly better in degenerative (p=0.001, MR grade: 1.4±0.9 in group 1 *vs.* 0.7±0.8 in group 2) and rheumatic (p=0.031, MR grade: 1.6±1.3 *vs.* 0.6±0.5) subgroups. However, there was no significant difference in terms of postoperative MR grade between rings in ischemic

Table 5
Evaluation of pre- and postoperative changes in echocardiographic parameters according to ring types

MR pathologies	Pre- *vs.* postoperative changes	Flexible Mean±SD	Rigid Mean±SD	*p*
Ischemic	Mitral regurgitation (°)	2.1±1.0	2.4±0.8	0.049*
	Left atrium (mm)	0.5±5.8	1.8±3.0	0.030*
	LVEDD (mm)	0.9±4.7	3.0±3.8	0.029*
	Ejection fraction (%)	-1.2±9.5	0.7±10.2	0.230
Degenerative	Mitral regurgitation (°)	2.4±1.0	2.9±1.1	0.001**
	Left atrium (mm)	0.1±6.9	3.5±4.6	0.005**
	LVEDD (mm)	0.9±5.9	4.1±5.3	0.014*
	Ejection fraction (%)	2.3±9.5	-0.5±8.1	0.177
Rheumatic	Mitral regurgitation (°)	1.8±1.4	3.0±1.0	0.023*
	Left atrium (mm)	-0.5±3.9	1.9±3.6	0.184
	LVEDD (mm)	2.1±7.5	3.2±6.5	0.488
	Ejection fraction (%)	1.9±8.7	0.6±14.4	0.777

SD: Standard deviation; LVEDD: left ventricular end diastolic diameter; * p≤0.05; ** p≤0.01.

subgroups (p=0.507). Significant improvement in NYHA was observed in both groups; nevertheless, a larger number of patients remained in NYHA class II-III in Group 1 (n=29, 13.7%) than in Group 2 (n=2, 2.2%).

Recurrent MR was detected in 27.9% of Group 1 and 11.4% of Group 2 at various grades. Recurrence mostly occurred within three to nine months following surgery. One patient was reoperated on the second postoperative day due to partial detachment of the annuloplasty ring. Severe late MR was observed in 22 (10.4%) patients in Group 1, whereas one (1.1%) was detected in Group 2. The reoperation rate for severe MR was 3.3% (n=7) and 1.1% (n=1) in Groups 1 and 2, respectively (p=0.293). The mean reoperation time was 12.9±8.3 months (median: 3 months). Predictors for recurrent MR by multivariate analysis were the degree of MR (p=0.038) and LVEDD (p=0.001, Table 4). There was no significant difference between ring types regarding recurrence-free survival (19.6±1.1 months in Group 1 *vs.* 19.5±0.7 months in Group 2, p=0.086, Figure 1). Reoperation-free survival was 35.0±0.4 months in Group 1 and 27.7±0.3 months in Group 2, and it showed no significant difference between groups (p=0.422, Figure 2).

DISCUSSION

The main goals of reconstructive surgery are the restoration of normal leaflet motion with a large surface of coaptation and stabilization of the annulus with remodeling annuloplasty.[7,8] Although various annuloplasty rings are available on the market, there is still lack of data on absolute assets of ring functions.[7,9] Flexible rings tend to preserve the contractile performance of LV; Yokote et al.[10] demonstrated that transverse diameter is more affected and did not restrain the annular mobility. Flexible rings can only be used for degenerative MV diseases. Rigid, downsizing rings have been associated with reduced risk of long-term recurrent MR in patients with ischemic or functional MR.[11,12] Despite these findings, it remains a matter of surgeon's preference. To tailor the selection of the annuloplasty ring, our patients were divided into subgroups according to the MV pathology and early and midterm changes in echocardiography and clinical status were evaluated. In Groups 1 and 2, rates of successful repair were acceptable (72% *vs.* 88.5%), the rate of immediate reoperation within 30 days was 0.3%, and the 30-day mortality rate was fair (9.2% *vs.* 10.4%) according to the period. Compared to a decade ago, it is usual to observe improvement in results with using pre-and perioperative TEE for anatomical details of the valve and the increasing experience of institutions. The majority of patients in our series showed notable improvement of their MR and symptom severity. To assess the effect of ring types on clinical outcomes, Khamooshian et al.[13] studied degenerative and ischemic MR patients by dividing them into three groups as rigid, flexible, and semi-rigid. They concluded that LVESD reduced with all rings, LVEDD only reduced with rigid and flexible, and LVEF did not alter. Similarly, our results projected that LVEF remained unchanged regardless of ring type. Additionally, the decrease of MR, LA size, and LVEDD was higher in Group 2 than in Group 1 in ischemic (MR, p=0.049; LA, p=0.030; LVEDD, p=0.029) and degenerative (MR, p=0.001; LA, p=0.005; LVEDD, p=0.014) subgroups (Table 5). The decrease in the degenerative subgroup was more significant compared to the ischemic subgroup due to the delay in remodeling in the presence of ischemic preconditioning. Although the decrease in MR was significant with rigid rings in the rheumatic subgroup (p=0.023), there was no nominal difference in LA size (p=0.184), LVEDD (p=0.488), and EF (p=0.777) among rings (Table 5). Given the fact that there was slightly more reduction with rigid rings, an overall reduction in the degree of MR was observed with both rings in all MR pathologies. Additionally, we have shown that the incidence observed for recurrent MR in the rigid ring group was significantly lower compared to the flexible ring group (28% *vs.* 11.5%, p<0.01). We believe that ring design might be one of the provocative reasons, especially in the presence of ischemic changes. Jensen et al.[14] concluded that saddle-shaped rings reduce strain on leaflets by uniform annular force distribution compared to flat rings. In our study, perioperative regurgitation up to Grade 2 with a gradient >5 mmHg was considered negligible. Recurrent MR was found to be the most common reason for reoperation.

In univariate analysis in our results, preoperative LVEDD, LVESD, LVEF, MR, ring type, ring number, and concomitant procedures were assessed for predictors of recurrency, and LVEDD (p=0.001), LVESD (p=0.001), and ring type (p=0.002) were found to be statistically significant. Cases having severe preoperative MR showed 3.065-fold higher risk of recurrency (odds ratio: 3.605, 95% confidence

interval: 0.902-10.409). In multivariate analysis, only preoperative MR (p=0.038) and LVEDD (p=0.001) became significant predictors for recurrent MR. Silberman et al.[12] searched for similar predictors in the univariate analysis, and preoperative LVESD and ring type were the predictors of late MR. There was no statistically significant difference between ring types on behalf of recurrence-free (p=0.086) and reoperation-free (p=0.422) survival. The main goal is to overcome the valvular pathology while improving the quality of life with preserved functional capacity. Arnaz et al.[15] reported a significant improvement in quality of life, and repair was found to be superior to replacement in terms of pain score. In our study, a significant improvement in NYHA was observed in both groups regardless of ring type at a follow-up period of 15.8±7.5 months (p=0.001).

There are limitations to this study. Due to its retrospective nature, data for particular fields, such as echocardiography records, may have been missing. Hence, the analyses could have been performed with available values. More detailed information should be added for better insight.

In conclusion, a saddle-shaped ring may expand the mechanical benefits rather than a flat ring by preserving the native mitral annular shape. Our study showed uniform results with both types of rings, improving NYHA class, reducing MR, and decreasing LV dimensions in patients undergoing MV repair. Routine intraoperative TEE should be performed to assess the success of repair for a better late outcome.

Ethics Committee Approval: The study protocol was approved by the Kartal Koşuyolu High Specialization Training and Research Hospital Clinical Research Ethics Committee (date: 27.03.2013, no: 2013/1.10). 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: Concept, design, data collection and analysis, writing and review: Ö.A.; Supervision, materials and analysis: S.S.; Concept and critical review: K.K.

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Cardiovascular Surgery and Interventions

Original Article Open Access

Could the echocardiographic parameters be a predictor to estimate cerebrovascular events in patients with micro-atrial fibrillation?

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ABSTRACT

Objectives: This study examined possible predictors of stroke [left atrial sphericity index (LASI), left atrial kinetic energy (LAKE), left atrial volume index (LAVI) atrial electromechanical delay (AEMD)] intervals in patients with micro-atrial fibrillation (micro-AF).

Patients and methods: A total of 102 consecutive patients (40 males, 62 females; mean age: 61.5±9.2 years; range, 18 to 75 years) diagnosed with micro-AF on rhythm Holter were included in this retrospective study between June 2021 and October 2021. Cranial magnetic resonance and computed tomography images of these patients were scanned from the hospital database. The patients were divided into two groups according to their stroke status (Group 1, the stroke group [n=25]; Group 2, the nonstroke group [n=77]). The LASI was calculated as a fraction of the left atrial maximum volume to the left atrial volume of the sphere in a four-chamber view. The biplane method of disks was used to calculate left atrium volume. The LAVI was calculated by dividing left atrium (LA) volume by the body surface area of patients. Atrial electromechanical delay intervals were calculated from the atrial walls by tissue Doppler imaging. These two groups were compared to assess whether echocardiographic parameters could be a predictor of cerebrovascular events.

Results: There was a statistically significant difference between Groups 1 and 2 in terms of left (75.7±4.5 *vs.* 68.4±3.5, p<0.001) and right (69.5±7.1 *vs.* 57±3.2, p<0.001) atrial lateral wall and LA medial wall (72±4 *vs.* 66.2±3.5, p<0.001) electromechanical delay times, LAVI (38.9±3.3 *vs.* 30.9±3.8, p<0.001), LASI (0.78±0.05 *vs.* 0.67±0.4, p<0.001), and LAKE (3.7±0.9 *vs.* 7.9±1.9, p<0.001), left atrial diameter (40±5 *vs.* 38±2, p<0.001).

Conclusion: Changes in LASI, LAVI, LAKE, left atrial diameter, and atrial AEMD times may be a predictor of stroke in patients with micro-AF.

Keywords: Atrial fibrillation, left atrial sphericity index, left atrial kinetic energy, micro-atrial fibrillation.

Atrial fibrillation (AF) is the most common type of sustained arrhythmia in clinical practice without P waves lasting a minimum of 30 sec. Atrial fibrillation increases total and cardiovascular mortality by 1.5 to 2.5 times.[1] It has been determined that the development of AF causes a five-fold increase in the risk of stroke. It has been observed that AF-related strokes have a more severe course than non-AF-related strokes.[2]

Atrial fibrillation is associated with structural and chronic diseases, such as hypertension, chronic kidney failure, heart failure, heart valve diseases, congenital heart defects, ischemic heart disease, diabetes, chronic obstructive pulmonary disease, hyperlipidemia, obesity, and thyroid hormone disorders. Atrial fibrillation begins as a result of hemodynamic or structural changes in the left atrium (LA), and during the paroxysmal and persistent phase, LA dilatation occurs, and mechanical functions gradually deteriorate.[3] Understanding the structure and function of the LA can be helpful in predicting the risk of developing AF and shaping treatment. It is not possible to accurately measure LA volumes from two-dimensional linear measurements of LA since LA expansion usually does not occur uniformly in all directions.

However, although calculating LA volume using magnetic resonance imaging (MRI) and cardiac computed tomography (CT) gives more accurate

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measurements, these are time-consuming and limiting procedures due to kidney and radiation damage.[3] Therefore, measurements made with transthoracic echocardiography (TTE) are vital in daily practice. Left atrial kinetic energy (LAKE) is a parameter that indicates left atrial mechanical function and can be calculated noninvasively with TTE.[4] Structural change in the atrium causes a delay between the electrical stimulation and mechanical contraction.

The atrial electromechanical delay (AEMD) is the time interval from the onset of the P wave on surface electrocardiography (ECG) to the beginning of the late diastolic wave on tissue Doppler (late distolic [Am] wave).[5,6] These structural changes also lead to a prolongation in P wave duration. Likewise, increases in the left atrial sphericity index (LASI) and left atrial volume index (LAVI) were also associated with increased AF recurrence.[7,8] The LASI was found to accurately indicate LA remodeling and accurately measure the spherical shape of the LA.[7]

Although there are many studies related to AF,[5,6] there are few studies on very short-lasting episodes of AF-like activity (micro-AF).[7,8] Sudden onset irregular tachycardia with ≥5 consecutive supraventricular episodes and a total absence of pulse and P waves lasting less than 30 sec have been defined as micro-AF in previous studies.[9,10]

Currently, there is limited information about the risk of shorter episodes of AF-like activity. Two studies have reported that supraventricular ectopic beats and supraventricular tachycardias may be associated with an increased risk of AF and stroke over time.[9,10] Currently, there are no recommendations on how to treat these patients. Hence, we examined possible predictors of stroke (LASI, LAKE, LAVI, and AEMD intervals) in patients with micro-AF.

PATIENTS AND METHODS

A total of 102 patients (40 males, 62 females; mean age: 61.5±9.2 years; range, 18 to 75 years) diagnosed with micro-AF by 24-h rhythm Holter monitoring were included in this retrospective study conducted at Faculty of Medicine Namık Kemal University, Department of Cardiology between June 2021 and October 2021. Clinical data were obtained by examining the database of our hospital. All blood samples of the patients were taken after 12 h of fasting. Patients diagnosed with paroxysmal AF in rhythm Holter monitoring, patients with structural valve disease, heart failure, thyroid hormone disorder, significant coronary artery disease, and a history of atherothrombotic stroke, lacunar infarction, or transient ischemic attack were excluded from the study.

In 24-h Holter monitoring (Schiller MT-101; Schiller AG, Baar, Switzerland), sudden onset of irregular tachycardia with ≥5 consecutive supraventricular episodes and the total absence of pulses and P waves lasting <30 sec was described as micro-AF. The patients were divided into two groups according to their stroke status (Group 1, those with stroke [n=25]; Group 2, those without stroke [n=77]). As a result of the examinations made in the database of our hospital, the diagnosis of stroke was made according to patient history, physical examination findings, cranial CT, and cranial MRI. Carotid Doppler ultrasonography, CT, or MRI angiography results of stroke patients were scanned to exclude the diagnosis of atherothrombotic stroke.

All patients underwent routine TTE with Vivid 5 (GE Healthcare, Wauwatosa, WI, USA) and an M4S Matrix array adult cardiac (3.5 MHz) probe on the lateral decubitus position. All assessments and measurements were made according to the European Association of Cardiovascular Imaging (EACVI) guidelines.[11] The area-length technique was used to calculate the LA maximum volume (LAV). Pulmonary veins and atrial appendages were not included in the measurement. Left ventricular ejection fraction was calculated according to the modified biplane Simpson method. The LAV and LA volume of sphere were calculated according to the following formulas: $LAV=(0.848\times LA\ area^{4chamber}\times LA\ area^{2chamber})/(\text{minimum LA length}/2)$;

$$\text{LA volume of sphere} = \frac{4}{3}\pi\left(\frac{\text{Maximum LA length}}{2}\right)3$$

$$\text{LASI} = \frac{\text{LA maximum volume}}{\text{LA volume of sphere}}.$$ [12]

The LASI was calculated as the ratio of LAV to LA volume of sphere. Left atrial kinetic energy was defined as 0.5×LA stroke volume (cm^3, volume at the beginning of left atrial systole-LA minimal volume) × 1.06 (g/cm^3, blood density) × (peak A velocity)^2.

In apical four-chamber view, pulse wave Doppler with a 3 mm sample volume was placed at the mitral leaflet tips, then the peak E and A waves were

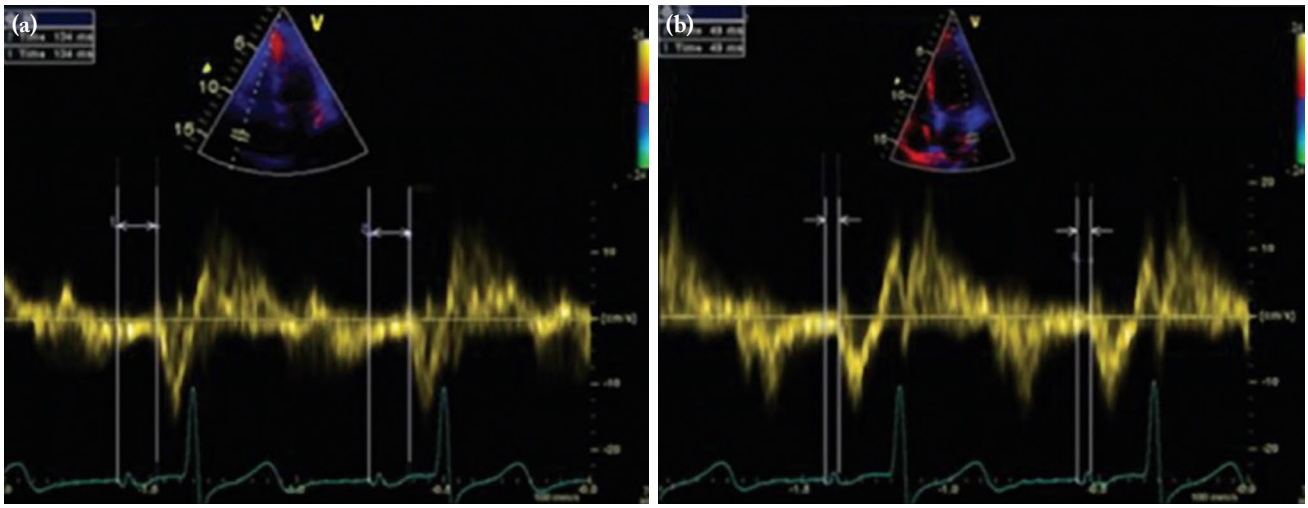

Figure 1. **(a)** Left atrium lateral atrial AEMD duration. **(b)** Right atrium lateral AEMD duration.
AEMD: Atrial electromechanical delay.

measured. Tissue Doppler imaging was performed on atrial walls in apical four-chamber view. The time interval from the onset of the P wave on ECG to the beginning of the Am wave was measured for AEMD from the atrial wall (Figure 1).

The time interval from the onset of the P wave on surface ECG to the beginning of the Am wave on tissue Doppler imaging was identified as AEMD (Figure 1a, b).[7] Atrial electromechanical delay intervals were defined as follows: lateral LA wall (LA lateral AEMD), interatrial septum (LA medial AEMD), and lateral right atrium (RA) wall (RA lateral AEMD). The differences between the LA lateral AEMD and RA lateral AEMD time intervals were expressed as inter-AEMD. Left intra-AEMD (intra-AEMDLEFT) was defined as the difference between LA lateral AEMD and LA medial AEMD. Right intra-AEMD (intra-AEMDRIGHT) was defined as the difference between LA medial AEMD and RA lateral AEMD.

Statistical analysis

All data were analyzed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution were reported as mean ± standard deviation (SD). Nonnormally distributed continuous variables were presented as median. Categorical variables were reported as percentages. Student's t-test was used to compare normally distributed data, and the Mann-Whitney U test was used for nonnormally distributed data. Categorical variables were compared using the chi-square test or Fisher exact test as appropriate. Univariate and stepwise logistic regression analyses were used to determine significant predictors of stroke in patients with micro-AF. The relationship between AEMD durations. LAVI, LASI, and LAKE was investigated using Pearson's correlation tests. The sensitivity and specificity of LASI, LAVI, LAKE, and AEMD durations to predict stroke in patients with micro-AF were analyzed by receiver operating characteristics (ROC) analysis. A p value <0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the patients were statistically similar, except for the CHA_2DS_2-VASc (C; Congestive heart failure, H; Hypertension, A2; Age ≥75 years, D; Diabetes mellitus, S2; Stroke, V; Vascular disease, A; Age 65-74 years, Sc; Sex category) score (Table 1). The CHA_2DS_2-VASc score was significantly higher in Group 1 than in Group 2 (4±1 *vs.* 2±1; p<0.001).

The AEMD times measured from atrial walls in Group 1 were longer (p<0.001). While the duration of intra-AEMDLEFT was longer in Group 1 than in Group 2 (4.56±2.04 *vs.* 3.78±1.53; p=0.039), inter-AEMD and intra-AEMDRIGHT

Table 1
Characteristics of the patients

Characteristics	All patients (n=102) n	%	Mean±SD	Median	Min-Max	Patients with stroke (n=25) Group 1 n	%	Mean±SD	Median	Min-Max	Patients without stroke (n=77) Group 2 n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			61.5±9.2					63.1±7.8					62.9±8.4			0.526†
Height (cm)			164.8±6.7					165.3±7.9					163.4±7.5			0.755#
Weight (kg)			79.7±10.7					78.4±11.4					80.4±12.1			0.416†
Sex																
Male	40	39.2				10	40				30	38.9				0.454#
Female	62	60.7				15	60				47	61.1				0.652#
Smoking	46	45				11	44				35	45.4				0.417#
Diabetes	60	58.8				15	60				45	58.4				0.511#
Hypertension	56	54.9				17	68				39	50.6				0.163#
Coronary artery disease	23	22.5				5	20				18	23.3				0.302#
Chronic heart failure	12	11.7				3	12				7	9				0.229#
CHA_2DS_2-VASc score			3±1					4±1					2±1			<0.001†
Laboratory data																
BUN (mg/dL)			22.5±10.8					23.2±8.4					22.6±9.7			0.446†
Creatinine (mg/dL)			0.8±0.1					0.82±0.1					0.78±0.1			0.106†
Total cholesterol (mg/dL)				222	33-446				220	117-260				228	133-446	0.063*
Triglyceride (mg/dL)				94.1	31-339				122	71-320				120.8	31-270	0.645*
HDL-C (mg/dL)				60	30-162				61	29-79				64	33-66	0.482*
LDL-C (mg/dL)			150.7±52.8					155.8±35.4					152.3±57.1			0.632†
Neutrophil ($\times10^3/\mu L$)				4.9	1.6-10.9				5.3	1.6-6.7				5.2	1.8-9.6	0.674*
Lymphocyte ($\times10^3/\mu L$)			3.4±1.3					3.7±0.4					3.2±1.3			0.547†
WBC ($\times10^3/\mu L$)				11.6	2.4-15.1				10.4	2.4-15				12.2	4.2-14.1	0.746*
Platelet ($\times10^3/\mu L$)			259.6±80.5					260.3±49.6					263±85.7			0.425†
Hemoglobin (g/dL)				13.2	9-17.1				13.3	10-17.1				13.2	10.6-17	0.529*
NT-pro BNP (pg/mL)				129	22-3463				117	22-1565				124	31-2134	0.228*
Glucose (mg/dL)				112	72-224				104	76-216				114	80-222	0.381*
AST (IU/L)				14	6-34				18.5	11-30				16	6-34	0.846*
ALT (IU/L)				17.6	6-41				20.2	13-31				16	6-41	0.066*
Na (mEq/L)				140	123-143				139	134-143				140	134-143	0.383*
K (mEq/L)				4.5	2.9-5.1				4.6	3.53-5.1				4.4	2.94-5.1	0.247*
TSH (mIU/L)				1.5	0.02-5.3				1.1	0.4-3.9				1.2	0.02-5.3	0.328*
T_4 (ng/dL)				1.2	0.02-5.3				1.2	0.9-1.8				1.2	0.02-4.1	0.873*
Medications																
ACEI	20.5	20				5	20				16	20.7				0.829#
ARB	47	46				15	44				32	41.5				0.277#
β-Blocker	50	49				12	48				38	49.3				0.058#
Ca–channel blocker	39	38.2				10	40				29	37.6				0.062#
Diuretic	33	32.3				8	32				25	32.4				0.445#
Acetyl salicylic acid	20	19.6				5	20				15	19.4				0.252#
Clopidogrel	21	20.5				5	20				16	20.7				0.656#
Oral antidiabetic	40	39.2				10	40				30	38.9				0.382#
Insulin	22	21.5				6	24				16	20.7				0.280#
Statin	22	21.5				4	16				18	23.3				0.103#

SD: Standard deviation; CHA_2DS_2-VASc score: C; Congestive heart failure, H; Hypertension, A2; Age≥75 years, D; Diabetes mellitus, S2; Stroke, V; Vascular disease, A; Age 65-74 years, Sc; Sex category; BUN: Blood urea nitrogen; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein cholesterol; WBC: White blood cell count; ProBNP: N-terminal fragment of the B-type natriuretic peptide precursor; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TSH: Thyroid stimulating hormone; T4: Thyroxine; ACE-I: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; # Chi-square test; * Mann-Whitney U; † Student's t-test.

Table 2
Comparison of echocardiographic data

	Group 1: Patients with stroke (n=25)			Group 2: Patients without stroke (n=77)			
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
LVEF (%)	60.3±5			60.5±3.5			0.456†
LAVI (mL/m^2)	38.9±3.3			30.9±3.8			<0.001†
LASI	0.8±0.1			0.7±0.0			<0.001†
LAKE (kdynes/cm^2)	3.7±0.9			7.9±1.9			<0.001†
LV end-diastolic diameter (mm)	47.7±3.8			46.5±2			0.207†
LV end-systolic diameter (mm)	30±3			32±2			0.257†
LA diameter (mm)	40±5			38±2			<0.001†
Mitral E velocity (m/s)	0.7±0.2			0.8±0.0			0.528†
Mitral A velocity (m/s)	0.6±0.1			0.6±0.0			0.655†
Atrial electromechanical delay measurements							
LA lateral AEMD	75.7±4.6			68.4±3.5			<0.001*
LA medial AEMD	72±4			66.2±3.6			<0.001*
RA lateral AEMD	69.5±7.1			57±3.2			<0.001*
Inter-AEMD		6.5	4-16.1		6.0	3.4-13.6	0.507†
Intra-AEMD left	4.6±2.0			3.8±1.5			0.039*
Intra-AEMD right	3.7±2.5			3.5±1.6			0.850*

SD: Standard deviation; LVEF: Left ventricular ejection fraction; LAVI: Left atrial volume index; LASI: Left atrial sphericity index; LAKE: Left atrial kinetic energy; LV: Left ventricle; LA: Left atrium; AEMD: Atrial electromechanical delay; RA: Right atrium; † Student's t-test; * Mann-Whitney U; p-value <0.005 was considered statistically significant.

times were similar in both groups (Table 2). The LAVI (p<0.001). LASI (p<0.001), and LA diameter (p<0.001) were statistically higher in Group 1. Left atrial kinetic energy was lower in Group 1 than in Group 2 (3.7±0.9 *vs.* 7.9±1.9; p<0.001). All other echocardiographic measurements were similar between the two groups.

In bivariate correlation analysis, a positive moderate-high level of correlation was observed between LASI and stroke (r=0.67, p<0.001). A positive high level of correlation was observed between AEMD times and stroke and LA medial AEMD (r=0.74, p<0.001), LA lateral AEMD (r=0.78, p<0.001), and RA lateral AEMD (r=0.78, p<0.001, Table 3). A high level of negative correlation was observed between LAKE and stroke (r=-0.71, p<0.001). In univariate logistic regression analysis, LASI, LAVI, LAKE, AEMD times, and CHA_2DS2-VASc scores were significant predictors of stroke in micro-AF (p<0.001 for all, Table 4).

In the stepwise logistic regression analysis, LAVI, LAKE in model 1, LAVI in model 2, LA diameter in model 3, CHA_2DS2-VASc score, LA lateral AEMD, LA diameter in model 4, LAKE,

Table 3
Correlation analysis between left atrial volume index, atrial electromechanical delay parameters and left atrial sphericity index and left atrial kinetic energy

	Stroke	
Parameter	r	*p*
LASI	0.67	<0.001
LAVI	0.78	<0.001
LAKE	-0.71	<0.001
LA lateral AEMD	0.78	<0.001
LA medial AEMD	0.74	<0.001
RA lateral AEMD	0.76	<0.001

LASI: Left atrial sphericity index; LAVI: Left atrial volume index; LAKE: Left atrial kinetic energy; LA: Left atrium; RA: Right atrium; AEMD: Atrial electromechanical delay.

Table 4
Univariate logistic regression analysis of predictors of stroke

	Univariate analysis		
	OR	95% CI	*p*
LAKE	0.211	0.108-0.409	<0.001
CHA_2DS_2-VASc score	2.292	1.558-3.373	<0.001
LAVI	3.05	1.672-5.591	<0.001
LASI	1.29	1.01-7.12	<0.001
LA diameter	2.15	1.587-2.930	<0.001
LA medial AEMD	1.738	1.347-2.243	<0.001
LA lateral AEMD	1.84	1.408-2.430	<0.001
RA lateral AEMD	1.549	1.259-1.907	<0.001

OR: Odds ratio; CI: Confidence interval; CHA_2DS_2-VASc score: CHA2DS2-VASc score: C; Congestive heart failure, H; Hypertension, A2; Age ≥75 years, D; Diabetes mellitus, S2; Stroke, V; Vascular disease, A; Age 65–74 years, Sc; Sex category; LAVI: Left atrial volume index; LASI: Left atrial sphericity index; LA: Left atrium; RA: Right atrium; AEMD: Atrial electromechanical delay.

Table 5
Multivariate stepwise logistic regression analysis for predictors of stroke

	Univariate analysis		
Variables	OR	95% CI	*p*
Model 1			
LAVI	2.05	1.048-4.023	0.036
LAKE	0.33	0.117-0.960	0.042
LA diameter	2.95	0.79-10.95	0.106
Model 2			
LAVI	2.20	1.113-4.353	0.023
LA diameter	2.07	0.997-4.314	0.051
CHA_2DS_2-VASc score	2.05	0.802-5.284	0.133
Model 3			
LA diameter	2.45	1.081-5.590	0.032
CHA_2DS_2-VASc score	4.5	1.538-13.168	0.006
LA lateral AEMD	2.19	1.109-4.335	0.024
Model 4			
LA diameter	2.92	1.320-6.689	0.009
CHA_2DS_2-VASc score	3.349	1.109-10.115	0.032
LAKE	0.371	0.190-0.724	0.004
Model 5			
LA diameter	2.268	1.289-3.992	0.005
CHA_2DS_2-VASc score	3.080	0.941-10.073	0.063
LASI	4.552	0.262-7.890	0.003
Model 6			
LA diameter	2.458	1.081-5.590	0.032
CHA_2DS_2-VASc score	4.500	1.538-13.168	0.006
LA lateral AEMD	2.193	1.109-4.335	0.024

OR: Odds ratio; CI: Confidence interval; LAVI: Left atrial volume index; LAKE: Left atrial kinetic energy; LA: Left atrium; CHA_2DS_2-VASc score: CHA2DS2-VASc score: C; Congestive heart failure, H; Hypertension, A2; Age ≥75 years, D; Diabetes mellitus, S2; Stroke, V; Vascular disease, A; Age 65-74 years, Sc; Sex category; AEMD: Atrial electromechanical delay; LAKE: Left atrial kinetic energy; LASI: Left atrial sphericity index;

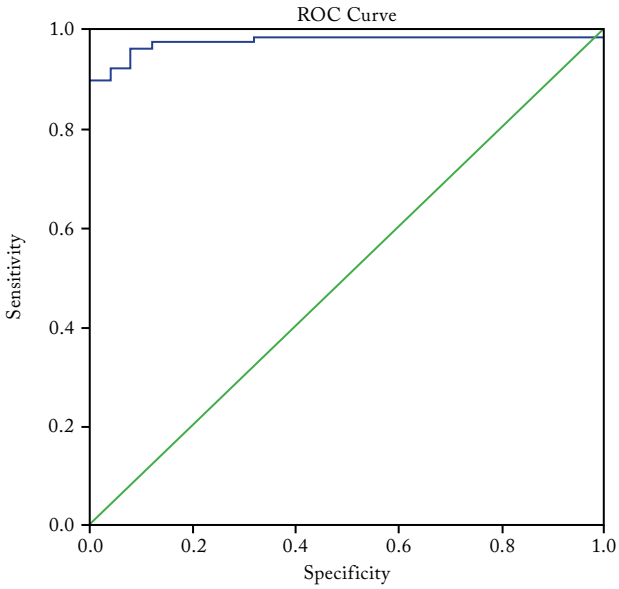

Figure 2. Receiver operating characteristics analysis performed to assess the predictive power of LAKE for stroke in patients with micro-AF.

LAKE: Left atrial kinetic energy; AF: Atrial fibrillation.

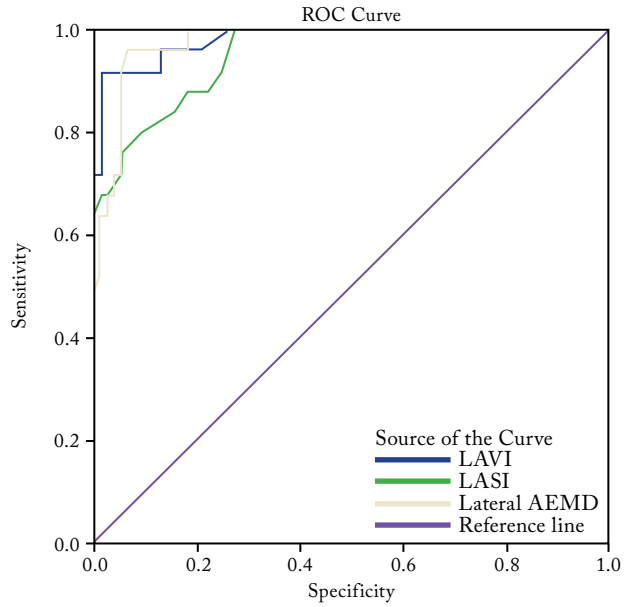

Figure 3. Receiver operating characteristics analysis performed to assess the predictive power of the AEMD durations, LASI and LAVI for stroke in patients with micro-AF.

AEMD: Atrial electromechanical delay; LASI: Left atrial sphericity index; LAVI: Left atrial volume index; AF: Atrial fibrillation; AEMD: Atrial electromechanical delay.

Table 6
Receiver operating characteristics curve analysis of independent predictors of stroke in patients with micro-AF

Variable	AUC	95% CI	Cut off value	*p*	Sensitivity (%)	Specificity (%)
LAKE	0.97	0.949-1.000	≤5.5	<0.001	96	92.2
LAVI	0.98	0.960-1.000	>36	<0.001	92	98.7
LASI	0.95	0.911-1.000	>0.71	<0.001	94	72.7
LA lateral AEMD	0.97	0.924-0.996	>70.4	<0.001	96	93.5

AF: Atrial fibrillation; AUC: Area under the curve; LAKE: Left atrial kinetic energy; LAVI: Left atrial volume index; LASI: Left atrial sphericity index; LA: Left atrium; AEMD: Atrial electromechanical delay.

CHA_2DS2-VASc score in model 5, LA diameter, LA diameter in model 6, CHA_2DS2-VASc score, and LA lateral AEMD were independent predictors for stroke (Table 5).

Lastly, a ROC analysis was performed to evaluate the predictive power of LASI, LAVI, LAKE, and LA lateral AEMD for stroke in patients with micro-AF (Figures 2 and 3; Table 6). The area under the curve and cut-off values were calculated for each parameter as follows: LASI (0.95, cut-off >0.71, p<0.001), LAVI (0.98, cut-off >36, p<0.001), LA lateral AEMD (0.97, cut-off >70.4, p<0.001), LAKE (0.97, cut-off ≤5.5, p<0.001).

DISCUSSION

This study investigated the significance of LASI, LAVI, AEMD, and LAKE indicators of left atrial electromechanical function as stroke markers in patients with micro-AF. Although there is a significant body of studies on stroke in patients with AF, these markers have not been studied before in a group of patients with micro-AF. Patients with atherothrombotic occlusion, lacunar infarction, and transient ischemic attack were also not included in our study, whereas patients with a high probability of cardioembolic stroke were included.

In a cohort study of ablated AF, the LA sphericity index was found to be an independent risk factor for arrhythmia recurrence.[7] In another study, patients with more spherical LA also had a more frequent history of thromboembolic events.[13] In a different study, healthy patients with 30 or more supraventricular ectopic beats had a three-fold increase in AF prevalence and a 60% increased risk of stroke and death after 6.3 years.[9] In the study by Tove Hygrell et al.,[14] the micro-AF group also had the highest cumulative incidence of stroke (4.1%) and death (10.3%). In previous studies, the prevalence of AF was found to be more than four times in the micro-AF group (13%) compared to the control group (3%).[7] Increasing LA pressure and volume for various reasons causes changes in LA shape.[11] The LA tries to provide optimum volume/surface area by becoming more spherical as an adaptation mechanism to reduce wall stress. Increased LA pressure expands the atrium along the atrial orthogonal axis, causing the shape of the atrium to change from oval to spherical.

Since the LA expands by different amounts in the three-dimensional plane, the LA volume and sphericity index can measure LA dimensions more accurately than linear measurements of LA.[11] Methods such as MRI and cardiac CT are invaluable for assessing asymmetric changes in LA.[11] However, the radiation exposure and time-consuming nature reduce the usability of these processes.

We observed that a higher LASI and LAVI, which means a more spherical LA, increases the risk of stroke. Therefore, close follow-up of patients with micro-AF with high LASI and LAVI in terms of stroke is essential. Deconstructed LA is more prone to the development of AF.[7] Left atrial kinetic energy, which is an important indicator of LA mechanical function, also decreases over time. Left atrial kinetic energy has been observed as a predictor of AF recurrence, independent of the LA diameter.[7] This proves that it is wrong to evaluate LA function by LA diameter alone, While electrical remodeling starts early in the AF process in the atria, structural remodeling is a late histopathological manifestation.[7]

The duration of AEMD is closely related to the histopathological changes in the atrium.[12] In particular, as reported in previous studies, the delay time in this conduction is greater in the lateral walls of the LA and left ventricle, which are further away from the sinus node.[7,15,16] Park et al.[15] found left atrial volumes and AEMD durations to be longer in patients with AF recurrence, supporting our study. In the study of Osmanagic et al.,[16] when the LASI value was taken as 0.9, the specificity was 79.3% and the sensitivity was 51.8% in predicting AF recurrence. Similarly, LASI was significantly higher in stroke patients with micro-AF in our study (0.78±0.05 in Group 1 *vs.* 0.67±0.04 in Group 2; p<0.001). It is important to provide rhythm control in the early period to prevent LA geometric remodeling and cardiovascular events that may occur due to AF. Predictors such as AEMD, LASI, LAKE, and LAVI will help us in early diagnosis before AF becomes permanent. In our study, we emphasized the importance of these indices in predicting stroke risk in patients with micro-AF.

How AF burden affects stroke risk is an ongoing discussion. A meta-analysis of studies in patients not using oral anticoagulant (OAC) therapy shows that patients with more persistent forms of AF rather than paroxysmal have a higher risk of stroke.[17] Atrial fibrillation progresses from the paroxysmal form to more permanent forms over time, and this situation increases with increasing age.[18] It is not known if high-risk individuals with micro-AF would benefit from OAC. However, these patients may benefit from risk-free interventions, primary prevention, optimizing lifestyle factors, and treating comorbidities as an effort to reverse atrial myopathy.

In the study by Binici et al.,[9] healthy individuals aged 55 to 75 years who underwent 48-h ECG monitoring were analyzed for supraventricular tachycardia (≥20 beats) and ≥30 supraventricular ectopic beats per hour. At the 6.3-year follow-up, they found a three-fold increase in the risk of developing AF and a 60% increase in the risk of death compared to the control group. It was determined that the number and duration of supraventricular beats were directly proportional in the development of AF. According to this study, OAC should not be started in patients with micro-AF and low supraventricular beats with a high risk of bleeding. In a Swedish cohort study, individuals free from AF were followed prospectively for >13 years.[19] Irregular SVTs without P waves showed the strongest association with clinical AF, with a cumulative incidence of 47.4%. Judging by studies and meta-analyses, there is no consensus on the treatment approach in patients with micro-AF. Oral anticoagulant therapy may be started in patients with micro-AF with a high CHA_2DS_2-VASc score, but prospective comprehensive studies are needed.

Comprehensive multicenter studies to be conducted in the future may lead to early initiation of medical treatment in patients with early AF risk. Therefore, these predictors are important in diagnosis and follow-up.

There are several limitations to this study. First, it was a single-center retrospective study with a small number of patients. Due to limited number of patients, the study cannot be attributed to the entire population. Second, there was a difference between the two groups in terms of the number of patients. Additionally, cardiac MRI and CT methods could be used in addition to TTE for LAVI and LASI calculations in patients with poor image quality. Lastly, longer Holter monitoring or a loop recorder could be fitted for patients with micro-AF on 24-h Holter recordings to detect paroxysmal AF attacks.

In conclusion, early diagnosis and treatment of micro-AF, which is the predictor of AF in the long term, is crucial. We can identify and treat these patients who are at risk of cardioembolic stroke with easily calculable indices. These new parameters may contribute to other parameters, such as CHA_2DS_2-VASc score and atrial diameters, in predicting cardioembolic stroke.

Ethics Committee Approval: The study protocol was approved by the Tekirdağ Namık Kemal University Ethics Committee (date: 28.12.2021. no: 2021.283.12.06). 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: Idea/concept, data collection and/or processing, analysis and/or interpretation, literature review, writing the article, materials: C.A.; Critical review, references and fundings, control/supervision: M.E.

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Usefulness of red cell distribution width as a predictor of amputation after embolectomy in acute lower limb ischemia

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ABSTRACT

Objectives: This study aimed to determine whether red cell distribution width (RDW) is an independent predictor of adverse outcomes in patients who underwent surgical embolectomy for acute lower limb ischemia.

Patients and methods: This retrospective study included 245 patients who underwent surgical embolectomy for acute lower limb ischemia between January 2008 and June 2012. Patients who had thrombosis of the atherosclerotic lesion and iliac or femoral stent thrombosis were excluded. The patients were divided into two groups according to the need for limb amputation after the initial embolectomy: 42 were in the limb amputation group (33 males, 9 females; mean age: 67.2±9.1 years; range, 52 to 85 years), and 203 were in the limb salvage group (132 males, 71 females; mean age: 58.4±9.3 years; range, 44 to 71 years). A multinomial logistic regression analysis was applied to determine the independent predictive effect of RDW and other parameters on major/minor amputation. The analysis was multivariately adjusted for age and sex to eliminate the confounding effect of other variables.

Results: Age (odds ratio [OR]=1.131, 95% confidence interval [CI]: 1.074-1.191, p<0.001), recurrent embolism in the same limb (OR=2.898, 95% CI: 1.238-6.780, p=0.01), urea level (OR=1.037, 95% CI: 1.013-1.062, p=0.003), and RDW (OR=1.324, 95% CI: 1.006-1.741, p=0.04) were significantly associated with the risk of major amputation in unadjusted multinominal logistic regression analysis, whereas the association of RDW with the risk of major amputation did not remain when adjusted for age and sex (OR=1.191, 95% CI: 0.963-1.474, p=0.10).

Conclusion: In conclusion, RDW may have a role in predicting adverse outcomes in patients treated for acute lower limb ischemia. However, it cannot be used as a stand-alone predictive marker.

Keywords: Acute lower limb ischemia, cardiovascular disease, peripheral artery disease, red cell distribution width.

Acute lower limb ischemia is a vascular emergency that occurs due to the sudden blockage of arterial blood perfusion to the limb and threatens limb viability. Despite advances in the management of cardiovascular diseases, the incidence of acute limb ischemia is still as high as 12 per 100,000 person-years due to the aging population. In addition, patients are at high risk of amputation and mortality, even if early revascularization is undertaken.[1,2] As an entity different from critical limb-threatening ischemia, which is characterized by collateral formation,[3] acute limb ischemia leads to rapid deterioration of the tissue metabolism. Uncompensated abrupt cessation of blood flow in the limb leads to ischemic inflammatory changes in all active tissues, such as skin, muscles, and nerves, which can progress to the gangrene of the limb if untreated.[4] Sudden occlusion of in-line arterial blood flow in the lower limb may be the result of an embolism from a remote source containing a thrombus (e.g., heart, abdominal aorta, or iliac arteries), or may result from the progression of a complicated atheroma plaque within the artery.[5] Although novel endovascular methods, such as percutaneous thrombolysis, thromboaspiration, and mechanical thrombectomy, have increasingly become applicable for complete or partial resolution of the occlusion over the last two decades, surgical embolectomy by a Fogarty balloon catheter remains an effective technique in the treatment of acute limb ischemia.[6]

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Amputation is the most dreadful complication after revascularization in patients presenting with acute lower limb ischemia. Although the time from arterial embolization to revascularization is of utmost vital importance,[7,8] it has been reported that a high score of ischemia, distal (below the knee) involvement, advanced age, the female sex, and anemia also predict amputation in acute lower limb ischemia.[1,9] Red cell distribution width (RDW), a laboratory indicator of anisocytosis, has recently been investigated for adverse outcomes in many clinical settings, and several studies have linked high RDW levels to high morbidity and mortality rates in atherosclerotic cardiovascular disease.[10,11] Although almost all of the studies have limitations that cannot definitively reveal a cut-off value of RDW to predict adverse outcomes, enough information has been provided to consider that RDW may be an additional laboratory marker during critical leg ischemia.[12,13] However, the relationship of RDW with limb salvage after acute lower limb ischemia has not been investigated yet. Since evidence has been provided that RDW is a risk factor for cardiovascular events, its diagnostic performance has been widely evaluated. Therefore, this study aimed to determine whether RDW is an independent predictor of adverse outcomes in patients who underwent surgical embolectomy for acute lower limb ischemia.

PATIENTS AND METHODS

This retrospective study was performed in the cardiovascular surgery department of a tertiary care hospital, and the study cohort was made up of 245 patients who underwent lower extremity embolectomy surgery between January 2008 and June 2012. Patients who had symptoms of acute critical limb ischemia, including new or worsening claudication or rest pain in the limb, paresthesia, paralysis, muscle weakness, or coldness in the extremity that continued for <7 days after the onset, and who underwent lower limb embolectomy surgery with the diagnosis of occlusive embolism were included in the study. Patients with acute lower limb ischemia symptoms due to thrombosis of the atherosclerotic lesion and patients with iliac or femoral stent thrombosis were excluded from the study. The patients were divided into two groups according to the need for limb amputation after the initial embolectomy: 42 were in the limb amputation group (33 males, 9 females; mean age: 67.2±9.1 years; range, 52 to 85 years), and 203 were in the limb salvage group (132 males, 71 females; mean age: 58.4±9.3 years; range, 44 to 71 years).

Preoperative diagnosis was made with ischemic findings in vascular physical examination and loss of normal triphasic arterial flow sound in femoral, popliteal, and below-the-knee pulses in the relevant extremity in portable Doppler ultrasound examination. The diagnosis of acute/subacute occlusive embolism, the location of the occlusive embolism, and the probable duration of the lesion were confirmed by color Doppler ultrasound. Digital subtraction angiography was performed in patients with suspected acute/subacute occlusion based on chronic peripheral arterial atherosclerotic disease (n=36, 15%). Demographic, clinical, and laboratory data of the patients were obtained by searching the archive records and the hospital's digital database and were recorded in the computer environment. Laboratory data included in the analysis were the results of total blood count and biochemistry sampled for preoperative preparation immediately after the decision for surgery was made. Red blood cell, RDW, and white blood cell parameters were routinely determined using a Siemens ADVIA 2120i hematology analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). The reference range of RDW at our hospital was %11.5-14.5.

Standard embolectomy procedure was performed in all patients using the appropriate diameters of Fogarty catheters (Edwards Lifesciences Corp., Irvine, CA, USA) with femoral artery or popliteal artery exploration according to the location of the embolism. The patients whose distal arterial flow was restored after the surgery and who had an improvement in the symptoms of critical leg ischemia were discharged to be followed up as outpatients. Reembolectomy was performed in patients whose distal perfusion was restored after embolectomy but then ceased again. In patients whose occlusive embolism did not improve despite the removal of the occlusive embolism, advanced angiographic examination was performed, and revascularization with a bypass graft was planned. Patients with worsening symptoms of critical limb ischemia and developing necrosis and gangrene after surgery were immediately scheduled for amputation. The level of amputation was jointly determined by vascular surgeons and orthopedic surgeons, and a balanced decision was made between healing the amputation stump without necrosis and leaving as much functional limb as possible. Major lower limb amputation was defined as amputation from any level

above the ankle, and minor lower limb amputation was defined as heel, metatarsal, or digital amputation below the ankle level. Follow-up data were obtained from rehospitalization archive files and outpatient visit records.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were presented as number (%). Normal distribution of the continuous parameters was tested using visual histograms and the Kolmogorov-Smirnov test or the Shapiro-Wilk test. To compare the continuous parameters between the two groups (limb amputation and salvage), the independent samples t-test was used if there was a normal distribution, and the Mann-Whitney U test was used if the distribution was nonnormal. For categorical variables, Fisher exact test was used when one or more cells in the contingency table had counts of less than five. A chi-squared test was used for other categorical variables. Since the amputation as the outcome variable is two-leveled (major and minor amputation), a univariate multinomial logistic regression analysis was applied to determine the independent predictive effect of RDW and other parameters on the outcome. The analysis was multivariately adjusted for age and sex to eliminate the confounding effect of these variables since advanced age had a significant effect on the outcome variable and the male sex was more frequent in patients who underwent amputation. The accuracy of RDW as a predictor of amputation was calculated using a receiver operator characteristic (ROC) curve. The area under the curve, sensitivity, and specificity was determined by the ROC curve. The point in the ROC curve closest to the top-left of the ROC graph was determined as the optimal cutoff value for RDW. A p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients were presented in Table 1. Mean age in the amputation group was significantly higher than in the amputation group (58.4±9.3 *vs.* 67.2±9.1 years for limb salvage and amputation groups, respectively; p<0.001). Male sex was more common in the amputation group, but the difference between the groups was not significant (132 [65%] *vs.* 33 [78.6%] for limb salvage and amputation groups, respectively; p=0.08). Cerebrovascular disease

Table 1
Baseline clinical characteristics of the patients

	Limb salvage group (n=203)			Amputation group (n=42)			
Variables	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)			58.4±9.3			67.2±9.1	**<0.001**
Sex							
Male	132	65		33	78.6		0.08
Diabetes	45	22.2		9	21.4		0.91
Hypertension	120	59.1		19	45.2		0.09
Coronary artery disease	61	30.0		8	19.0		0.14
Tobacco use	128	63.1		18	42.9		**0.01**
Chronic obstructive pulmonary disease	58	28.6		16	38.1		0.22
Cerebrovascular disease	27	13.3		16	38.1		**<0.001**
Renal failure	42	20.7		10	23.8		0.65
Site of arterial embolism							
Abdominal aorta	14	6.9		2	4.8		0.46
Iliac arteries	37	18.2		12	28.6		0.12
Femoral arteries	152	74.9		28	66.7		0.27
Recurrent embolism	41	20.2		18	42.9		**0.002**

SD: Standard deviation.

was significantly more common in the amputation group (27 [13.3%] *vs.* 16 [38.1%] for limb salvage and amputation groups, respectively; p<0.001), and tobacco use was significantly less common in the amputation group (128 [63.1%] *vs.* 18 [42.9%] for limb salvage and amputation groups, respectively; p=0.01). The proportion of patients requiring embolectomy due to recurrent embolism was significantly higher in the amputation group than in the limb salvage group (41 [20.2%] *vs.* 18 [42.9%] for limb salvage and amputation groups, respectively; p=0.002).

Of the 245 patients who underwent embolectomy for lower extremity embolism, 42 (17.1%) patients underwent amputation of the same limb; of these, 26 (10.6%) were major lower limb amputations (14 early in-hospital amputations, 12 postdischarge follow-up amputations), 16 (6.5%) were minor amputations (12 early in-hospital amputations, four postdischarge follow-up amputations).

Total blood count and biochemical parameters did not differ significantly between the limb salvage and amputation groups, except for the RDW (13.7±1.7% *vs.* 14.5±1.1%, p<0.001), platelet distribution width (22.3±12.7 *vs.* 24.2±14.0 fL, p=0.03), and urea (38.2±12.9 *vs.* 46.1±18.7 mg/dL, p=0.001, Table 2). The mean RDW was 13.80±1.17% in

Table 2
Comparison of baseline laboratory parameters of the patients

	Limb salvage group (n=203)	Amputation group (n=42)	
Variables	Mean±SD	Mean±SD	*p*
Hemoglobin (g/dL)	14.0±1.6	14.4±1.5	0.19
Hematocrit (%)	42.0±5.1	42.4±4.7	0.97
MCV (fL)	88.0±5.0	89.5±5.8	0.11
MCH (pg)	29.4±1.9	29.8±1.6	0.46
MCHC (g/dL)	33.2±1.0	33.4±1.0	0.23
RDW (%)	13.7±1.7	14.5±1.1	<0.001
Platelet count (K/uL)	261.6±66.4	252.6±88.2	0.15
MPV (fL)	8.2±1.1	8.2±1.1	0.71
PDW (fL)	22.3±12.7	24.2±14.0	0.03
WBC (K/uL)	8.2±2.2	7.8±3.3	0.10
Neutrophil count (K/uL)	5.3±1.9	5.0±2.1	0.19
Neutrophil percentage (%)	61.4±9.9	61.2±12.0	0.45
Lymphocyte count (K/uL)	2.2±0.7	2.0±0.6	0.08
Monocyte count (K/uL)	0.6±0.2	0.6±0.3	0.19
Glucose (mg/dL)	135.0±58.2	134.0±51.9	0.66
Urea (mg/dL)	38.2±12.9	46.1±18.7	0.001
Creatinine (mg/dL)	1.0±0.5	1.0±0.5	0.95
ALT (U/L)	26.3±15.6	27.3±23.1	0.39
AST (U/L)	24.5±12.1	23.0±13.6	0.08
PT	12.4±3.5	12.8±4.4	0.24
aPTT	33.7±12.1	42.3±47.3	0.11
Free T3 (pg/dL)	2.9±0.6	2.8±0.5	0.53
Free T4 (ng/dL)	1.3±0.5	1.4±0.5	0.98
TSH (μIU/mL)	1.8±1.1	1.7±1.4	0.31

SD: Standard deviation; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width; WBC: White blood cell count; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; TSH: Thyroid-stimulating hormone.

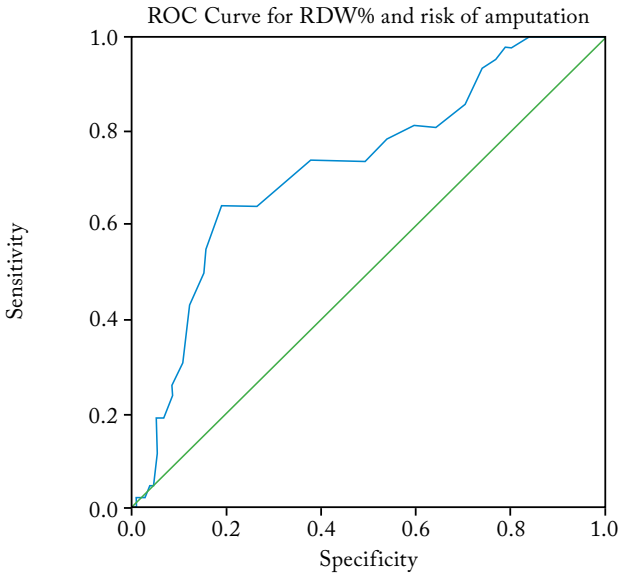

Figure 1. Receiver operating characteristics curve for RDW and risk of amputation.
ROC: Receiver operator characteristic; RDW: Red cell distribution width.

females and 13.85±1.83% in males (p=0.95). Receiver operating characteristics curve for RDW and risk of amputation revealed an area under the curve of 0.725 (95% confidence interval [CI]: 0.640-0.811, p<0.001) and an optimal cut-off value of 13.85% (sensitivity 69%, specificity 68%; Figure 1). Both visual inspection and the area under the curve value suggest that the fit of the model is in the acceptable range. The results suggest that the RDW score was efficient for identifying amputation.

In univariate (unadjusted) multinomial logistic regression analysis, age (odds ratio [OR]=1.131, 95% CI: 1.074-1.191, p<0.001), recurrent embolism in the same limb (OR=2.898, 95% CI: 1.238-6.780, p=0.01), urea level (OR=1.037, 95% CI: 1.013-1.062, p=0.003), and RDW (OR=1.324, 95% CI: 1.006-1.741, p=0.04) were significantly associated with the risk of major amputation, whereas the association of RDW with the risk of major amputation did not remain when adjusted for age and sex (OR=1.191,

Table 3
Univariate multinominal logistic regression analysis and multivariate multinomial logistic regression analysis adjusted for age and sex

	Univariate analysis unadjusted			Multivariate analysis (adjusted for age and sex)		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
Age (year)						
Major amputation	1.131	1.074-1.191	<0.001			
Minor amputation	1.074	1.016-1.136	0.01			
Cerebrovascular disease						
Major amputation	1.956	0.721-5.306	0.18	0.559	0.174-1.799	0.33
Minor amputation	10.864	3.652-32.319	<0.001	9.296	2.723-31.734	<0.001
Recurrent embolism						
Major amputation	2.898	1.238-6.780	0.01	3.862	1.460-10.216	0.006
Minor amputation	3.073	1.080-8.742	0.03	3.726	1.260-11.024	0.01
Urea (mg/dL)						
Major amputation	1.037	1.013-1.062	0.003	1.038	1.010-1.066	0.006
Minor amputation	1.024	0.992-1.057	0.14	1.016	0.984-1.049	0.33
RDW (%)						
Major amputation	1.324	1.006-1.741	0.04	1.191	0.963-1.474	0.10
Minor amputation	1.239	0.907-1.691	0.17	1.131	0.859-1.489	0.38
PDW (fL)						
Major amputation	0.999	0.967-1.032	0.97	0.995	0.960-1.031	0.78
Minor amputation	1.024	0.991-1.059	0.14	1.029	0.994-1.065	0.10

OR: Odds ratio; CI: Confidence interval; RDW: Red cell distribution width; PDW: Platelet distribution width.

95% CI: 0.963-1.474, p=0.10). Age (OR=1.074, 95% CI: 1.016-1.136, p=0.01), cerebrovascular disease (OR=10.864, 95% CI: 3.652-32.319, p<0.001), and recurrent embolism (OR=3.073, 95% CI: 1.080-8.742, p=0.03) were significantly associated with the risk of minor amputation, and cerebrovascular disease (OR=9.296, 95% CI: 2.723-31.734, p<0.001) and recurrent embolism (OR=3.726, 95% CI: 1.260-11.024, p=0.01) remained significant even when adjusted for age and sex (Table 3). Post hoc power analysis revealed that, given an alpha error of 0.05, the two-tailed difference in mean RDW between groups yielded a statistical power of 89.39%.

DISCUSSION

This study aimed to test whether RDW can predict the risk of amputation in the early postoperative or midterm period in patients who underwent embolectomy for acute lower limb ischemia. The mean RDW in the amputation group was within the normal range but was significantly higher than that of the patients in the limb salvage group. In the univariate analysis, RDW was found to be a significant predictor of major amputation but not that of minor amputation. In the multivariate analysis adjusted for age and sex, this significant association was absent. The overall amputation (major and minor amputations or early and midterm amputations) sensitivity and specificity of RDW as a laboratory indicator was unsatisfactory.

It is controversial whether the ideal interventional treatment in acute lower limb ischemia is the use of evolving endovascular methods or the traditional surgical approach. Lukasiewicz,[9] in a recent study comparing the results of endovascular procedures and surgery/hybrid therapy in acute limb ischemia, reported that amputation and complication rates were comparable, six-month mortality was higher in those who underwent surgery, and the rate of reintervention was higher in those who underwent endovascular treatment. This study concludes that both modalities have an effective role in the contemporary management of acute lower limb ischemia, with two-thirds of all patients having arterial thrombus in the etiology (half underwent surgery) and embolism (86% underwent surgery) in the remaining. Surgery has been our routine approach in cases with arterial embolism from a distal source to the lower limb, and in the present study, we wanted to determine the prognostic role of RDW in this patient subgroup; our early amputation rate (n=26, 10.6%) was close to the rate reported after surgery in the above study (8.9%).

Several studies have addressed clinical and demographic risk factors for amputation following acute lower limb ischemia, but the parameters reported were varied. In a recent epidemiological study, the one-year amputation rate was as high as 46%, and high-grade ischemia, the female sex, age, and anemia were associated with a higher risk of amputation. In addition, this study reported that the amputation rate in individuals living at a nursing home was 100%.[1] There were also studies reporting that delayed surgical intervention after admission significantly increased the risk of amputation.[7,14] In our study, recurrent embolism in the related limb and urea level appeared to be significant predictors of both major and minor amputations, even when adjusted for age and sex.

Red cell distribution width reflects the erythrocyte size distribution and is routinely calculated in the total blood count. Although it is used in the differential diagnosis of anemia, it has been shown to be correlated with fragility and vulnerability in individuals with systemic disease. Therefore, its usefulness in calculating cardiovascular risk has recently been the focus of research.[15] Talarico et al.,[10] in a retrospective study, found that the highest RDW tertile was independently associated with increased risk of all-cause death (hazard ratio [HR]=2.73, 95% CI: 1.63-4.5) and composite end point (adjusted HR=2.23, 95% CI: 1.53-3.24), (Cox regression, median follow-up: 3.78 years), proposing that RDW is a good prognostic marker for cardiovascular mortality. Others reported that the increased values of RDW were significantly associated with several cardiovascular outcomes, including coronary calcium score and related cardiovascular risk,[11] periprocedural myocardial infarct in patients receiving elective percutaneous coronary intervention,[16] mortality due to carotid atherosclerosis,[17] and stroke risk.[18]

A survey study demonstrated that RDW is an independent predictor of the risk of developing peripheral artery disease. The study determined that even when multiconfounding adjustment was made, each unit increase in the RDW increased the risk of peripheral arterial disease. Finding Odd's ratio 1.9 was a numerical indicator of this. In fact, the high quartile RDW was found to significantly improve the predictive accuracy of peripheric arterial disease

screening criteria.[14] Ye et al.,[19] in a study in which they followed 13,039 patients with peripheral artery disease, showed that patients in the highest quartile of RDW had a 66% higher overall mortality than those in the lowest quartile (after adjustment for age, sex, cardiovascular risk factors, and comorbidities). Another more recent study suggested that an RDW level above the 75th percentile (>14.1%) is an independent predictor of peripheral artery disease presence and complexity (TASC [TransAtlantic InterSociety Consensus] C and D).[20] Although these studies reliably indicate that RDW levels are indicative of the presence and prognosis of lower extremity ischemic artery disease, none of them have addressed whether RDW levels are associated with limb salvage after acute lower limb ischemia.

Since the cut-off value we found (13.85%) for the prediction of overall (major and minor) amputation is in the normal range, it may not have prognostic significance alone in patients presenting with acute lower limb ischemia. Red cell distribution width is used in routine clinical practice in the differential diagnosis of vitamin B12 deficiency, folic acid deficiency, and other megaloblastic anemias with macrocytosis. Therefore, RDW can be affected by the level of these substances. Moreover, although the upper limit of RDW is reported as 14.0%, this value is an instrument-specific value and may vary according to the standards of each laboratory. In addition to these, considering that RDW is affected by acute inflammation, white blood cell count, and even lipid profile, it can only aid other prominent risk factors in calculating the risk of amputation after acute limb ischemia.[21]

The main limitation of the present study was its retrospective design. In a prospective and match-controlled study, the deviation of RDW from the normal value could be calculated, and a more accurate effect size could be obtained. Another limitation of the study was that the operations were performed by different surgeons, which may have affected the patency. The inability to include amputation-free survival rates in the risk calculation due to the short follow-up period is one of the limitations that should be noted. Because of the heterogeneity in our patient group, RDW levels may not have accurately predicted the risk of amputation in our study. A larger study in a more homogeneous group is required.

In conclusion, RDW may have a role in the prediction of adverse outcomes in patients treated for acute lower limb ischemia; however, since amputation is associated with many confounders and RDW levels are affected by certain clinical parameters, it cannot be used as a stand-alone predictive marker. Future studies on risk assessment in amputation are needed, in which the confounders are adjusted and the RDW values are calibrated with a control group sampled at the same health center, to determine the optimal cut-off value or percentile of RDW.

Ethics Committee Approval: The study protocol was approved by the Türkiye Yüksek Ihtisas Education and Research Hospital Education Planning Board (date: 23.09.2014, no: 12631). 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: Data collection and/or processing, analysis and/or interpretation, literature review, writing the article, critical review, references and fundings: S.S.; Idea/concept, design: I.T.

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Radiofrequency ablation versus high ligation and stripping for the treatment of symptomatic great saphenous vein insufficiency: Short-term patient-reported outcomes

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ABSTRACT

Objectives: The study aimed to compare short-term patient-reported outcomes of radiofrequency ablation (RFA) versus high ligation and stripping (HLS) in a cohort with symptomatic great saphenous vein (GSV) insufficiency.

Patients and methods: This was a single-institution, retrospective, observational, cohort study of prospectively collected data. All procedures were performed between January 2019 and February 2021. Ninety-seven patients (54 females, 43 males; mean age: 45.2±11.1 years; range, 18 to 76 years) with lower limb chronic venous disease symptoms refractory to exercise, compression stockings, and pharmacotherapy underwent RFA (n=60) or HLS (n=37). Self-reported pain assessment was performed on the first postoperative day using the numeric rating scale, and duration of return to daily activities was questioned on the 30th postoperative day.

Results: Patients in the RFA group reported significantly less pain compared to patients in the HLS group with median numeric rating scale scores of 1.5 (0-4) versus 4 (2-5), respectively (p<0.001). The RFA group returned to their daily routine significantly sooner compared to the HLS group (1 [1-1] versus 1.5 [1-4] days, respectively; p=0.004).

Conclusion: Radiofrequency ablation is associated with significantly less postoperative pain and earlier return to daily activities compared to HLS in patients with symptomatic GSV insufficiency.

Keywords: Chronic venous disease, great saphenous vein insufficiency, high ligation and stripping, numeric rating scale, radiofrequency ablation.

Lower limb chronic venous disease (CVD) is a progressive and persistent condition that affects superficial, deep, and perforating venous pathways of the lower limbs.[1-3] With an estimated prevalence of 60 to 80%, CVD is responsible for at least 2% of the annual healthcare costs in developed countries.[2,3]

The main pathophysiological mechanism includes compromised venous return toward the right heart with subsequent blood reflux through involved venous segments.[2] Chronic venous reflux causes edema and structural changes in interstitial tissues and creates clinical symptoms associated with CVD.[2,3]

High ligation and stripping (HLS) has been the historical gold standard modality for the treatment of symptomatic patients who have axial great saphenous vein (GSV) reflux with or without saphenofemoral junction reflux, whereas newer thermal ablation techniques, including radiofrequency ablation (RFA), are being more and more commonly adopted.[4] Previous research has shown improved clinical outcomes after RFA in patients with CVD; however, patient-reported outcomes remain relatively understudied.[5,6] The present study aimed to compare short-term patient-reported outcomes of RFA versus HLS in a cohort with symptomatic GSV insufficiency.

PATIENTS AND METHODS

This was a single-institution, retrospective, observational, cohort study of prospectively collected data. All procedures were performed at the Department of Cardiovascular Surgery, Kartal Dr. Lütfi Kırdar City Hospital between January 2019 and February 2021. Consecutive patients who underwent surgery for lower limb CVD due to superficial vein incompetency were assessed for possible enrollment. Inclusion

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criteria were the existence of symptomatic lower limb venous insufficiency with duplex ultrasound (DUS) confirmation, Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) class C2-6 disease, and undergoing surgery for GSV insufficiency with either RFA or HLS. Exclusion criteria were being younger than 18 years of age, pregnancy, CEAP class C1 disease, undergoing surgery for small saphenous vein insufficiency, having CVD symptoms due to suprainguinal pathology, history of deep venous thrombosis, and undergoing treatment with any modality other than RFA or HLS (e.g., laser ablation, cyanoacrylate ablation, foam sclerotherapy, or mechanochemical ablation). A total of 103 patients were assessed for eligibility. After the exclusion of 6 patients, the remaining 97 patients (54 females, 43 males; mean age: 45.2±11.1 years; range, 18 to 76 years) who fulfilled the criteria were included in the study. Of these patients, 37 undergoing HLS made up the HLS group, and 60 patients undergoing RFA made up the RFA group (Figure 1). Patients were followed-up for 30 days.

Diagnosis and treatment

Patients with lower limb CVD symptoms refractory to exercise, compression stockings, and pharmacotherapy underwent DUS imaging in the upright position. Those who had grade 3 or 4 GSV incompetency were considered candidates for intervention. Disease severity was scored using CEAP classification and the Venous Clinical Severity Scale (VCSS). Patients with a GSV diameter of ≥5.5 mm at thigh level without focal dilation were offered to undergo RFA or HLS, and patients with a GSV diameter of <5.5 mm were offered to undergo HLS. Treatment modality was chosen following a patient-surgeon discussion including current evidence of short- and long-term outcomes and possible recurrence mechanisms. Preoperative surgeon-performed, duplex-guided vein mapping was done to mark incompetent GSV segments, incompetent perforators, and superficial varicosities in the upright position. Procedures were performed under general, spinal, or local anesthesia with real-time DUS guidance. Tumescent anesthesia was routinely used during RFA. Thermal ablation was performed at 120˚C in 7-cm segments starting 2 cm distally to the saphenofemoral junction in accordance with the manufacturer's recommendations (ClosureFast RFA System; Medtronic Inc., Minneapolis, MN, USA). Saphenofemoral junction tributaries were ligated during HLS. Perforating veins with reflux flow were ligated where needed, and superficial varicosities were treated by multiple stab phlebectomies during the same session. Patients were encouraged to mobilize as soon as possible after surgery. Treated legs were wrapped with elastic bandages for 24 h, and patients were advised to wear compression stockings afterwards.

Follow-up

All patients were seen at the outpatient clinic on the first, seventh, and 30th postoperative days. Procedural success was evaluated by DUS imaging and was defined as obliteration of the treated GSV segment. Complications were noted. Self-reported pain assessment was performed on the first postoperative day by instructing patients to mark the degree of pain on a numeric rating scale (NRS). The NRS is a scale designed to help patients report their pain level by circling a number from 0 to 10 on a paper strip with

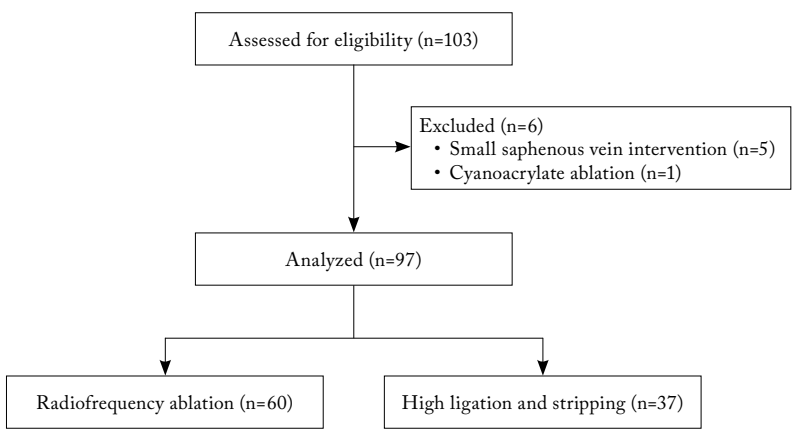

Figure 1. Flow diagram.

0 meaning "no pain" and 10 meaning "the worst pain you ever experienced." On the 30th postoperative day, patients were also questioned for the duration taken to return to daily activities by the question, "How many days did it take you to return to your normal daily activities after the procedure?"

Statistical analysis

Statistical analyses were performed using Jamovi version 2.2.5.0 (The Jamovi Project, Sydney, Australia). Qualitative variables were presented as absolute numbers (n) and frequencies (%). Frequencies were compared using Pearson's chi-squared test or Fischer exact test depending on expected number of observations. Histograms and the Shapiro-Wilk test were used for normality assessment of quantitative variables. Normally distributed quantitative variables were presented as mean ± standard deviation, and nonnormally distributed quantitative variables were presented as median and interquartile range. Means were compared using Student's or Welch's t-test according to the homogeneity of variances, and medians were compared using the Mann-Whitney U test. The level of statistical significance was set at a p value of <0.05.

RESULTS

The two groups were balanced in terms of demographics and comorbidities (Table 1). Thirty-eight (64.4%) patients in the RFA group had CEAP C2 disease, whereas 25 (69.4%) patients in the HLS group had CEAP C2 disease on physical examination (p=0.223). Venous Clinical Severity Scale scores were similar between groups (9.5 [7-12] in the RFA group *vs.* 8.5 [6.25-11] in the HLS group, p=0.270). Preoperative DUS revealed Grade 4 venous reflux in 58 (96.7%) patients in the RFA group and in 35 (94.6%) patients in the HLS group (p=0.635). The median GSV diameter was significantly larger in the RFA group (6.5 [5.7-8] mm *vs.* 5.45 [4.15-7.67] mm, p=0.005, Table 2).

Fifty-six (93.3%) patients in the RFA group received segmental treatment (55 above-knee and one below-knee ablation), whereas 11 (29.7%) patients in the HLS group underwent segmental treatment (11 above-knee stripping; p<0.001). Majority of patients in both groups were operated on with spinal or local anesthesia (57 [95%] patients in the RFA group *vs.* 34 [91.9%] patients in the HLS group, p=0.671, Table 2).

Table 1
Patient demographics

	All patients (n=97)					Radiofrequency ablation (n=60)				High ligation and stripping (n=37)				
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	p
Age (year)			45.2±11.1					45.2±10.1					45.1±12.7			0.945[a]
Female sex	54	55.7				32	53.3				22	59.5				0.555[b]
Hypertension	16	16.5				11	18.3				5	13.5				0.534[b]
Diabetes	16	16.5				10	16.7				6	16.2				0.954[b]
Body mass index (kg/m^2)				27.5	24.8-31.1				27.2	25-31.6				27.8	24.1-30.3	0.294[c]

SD: Standard deviation; IQR: Interquartile range; a: Student's t-test; b: Pearson's chi-squared test; c:Mann-Whitney U test.

Table 2
Operative details

	All patients (n=97)				Radiofrequency ablation (n=60)				High ligation and stripping (n=37)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
CEAP class													0.223[a]
C2	63	66.3			38	64.4			25	69.4			
C3	19	20			10	16.9			9	25			
C4	5	5.3			3	5.1			2	5.6			
C5	3	3.2			3	5.1			0	0			
C6	5	5.3			5	8.5			0	0			
VCSS score			9	7-12			9.5	7-12			8.5	6.25-11	0.270[b]
Venous reflux													0.635[c]
Grade 3	4	4.1			2	3.3			2	5.4			
Grade 4	93	95.9			58	96.7			35	94.6			
Vein diameter (mm)			6.4	5.35-7.9			6.5	5.7-8			5.45	4.15-7.67	**0.005*[b]**
Treated segment													**<0.001*[a]**
Complete GSV	30	30.9			4	6.7			26	70.3			
Above- or below-knee GSV	67	69.1			56	93.3			11	29.7			
Type of anesthesia													0.671[c]
General	6	6.2			3	5			3	8.1			
Regional/local	91	93.8			57	95			34	91.9			

IQR: Interquartile range; CEAP: Clinical, Etiological, Anatomical, and Pathophysiological; VCSS: Venous Clinical Severity Scale; GSV: Great saphenous vein; a: Pearson's chi-squared test; b: Mann-Whitney U test; c: Fisher exact test; * p<0.05.

Surgical success was achieved in all patients. No patients were lost to follow-up. Patients in the RFA group reported significantly less pain compared to patients in the HLS group with median NRS scores of 1.5 (0-4) versus 4 (2-5) (p<0.001). The RFA group returned to their daily routine significantly sooner compared to the HLS group (1 [1-1] *vs.* 1.5 [1-4] days, p=0.004). Median length of hospital stay and complication rates were statistically similar between groups (Table 3).

DISCUSSION

Results of the present study demonstrate that patients undergoing RFA for the treatment of GSV insufficiency experience significantly less pain on the first postoperative day, and they return to their daily routine significantly sooner compared to patients undergoing HLS. Our analysis also revealed excellent success rates for both procedures in a 30-day follow-up. These findings correlate with previous research reporting better or comparable short- and long-term outcomes with RFA compared to HLS.[7-9] In a randomized clinical trial of 88 patients, Subramonia and Lees[7] concluded that RFA was superior to HLS in terms of short-term outcomes, including postoperative pain and time to return to full level of household activities. However, they also concluded that this superiority would not be significant in the long term if recurrence and risk of reoperation were taken into account.[7] Another randomized clinical trial by Helmy ElKaffas et al.[8] reported lower complication rates for RFA in the short term and similar recurrence rate in the long term compared to HLS. Shaikadov et al.[9] revealed that patients undergoing RFA had significantly less postoperative pain compared to patients undergoing HLS in their multicenter analysis. One-year recurrence rates were also reported to be similar in that study.[9] We only had 30-day follow-up data, therefore cannot comment on long-term success rates.

Both groups had similar clinical and radiological features except for a significantly larger median GSV diameter in the RFA group. This significant difference was a direct result of reimbursement regulations regarding endovenous RFA treatment, as the Social Security Institution requires patients to have a GSV diameter of ≥5.5 mm for the compensation of an RFA device. Although it was not an objective of our study, considering that patients with larger and smaller veins

Table 3
Outcomes and complications

	All patients (n=97)				Radiofrequency ablation (n=60)				High ligation and stripping (n=37)				*p*
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	
Obliteration of the treated segment	97	100			60	100			37	100			
NRS			2	0-5			1.5	0-4			4	2-5	**<0.001**[*a]
Return to daily activities (day)			1	1-2			1	1-1			1.5	1-4	**0.004**[*a]
Length of hospital stay (day)			1	1-1			1	1-1			1	1-1	0.128[a]
DVT	0	0			0	0			0	0			
Superficial phlebitis	3	3.1			1	1.7			2	5.4			0.556[b]
Infection	2	2.1			1	1.7			1	2.7			1.000[b]
Skin burn	2	2.1			1	1.7			1	2.7			1.000[b]
Focal paresthesia	1	1.0			0	0			1	2.7			0.381[b]

IQR: Interquartile range; NRS: Numeric rating scale; DVT: Deep vein thrombosis; a: Mann-Whitney U test; b: Fisher exact test; * p<0.05.

(RFA and HLS groups, respectively) had similar demographic, clinical, and radiological findings and outcomes, our results show that vein diameter should not be an indicator of necessity for intervention for venous insufficiency. A prospective cohort study from a national registry reported similar results.[10] They compared CEAP classes, VCSS scores, and patient-reported outcomes before and after treatment in patients with a vein diameter of ≥5 mm versus <5 mm, revealed similar symptomatic improvement rates between groups, and concluded that patients should not be denied for intervention based on vein size.[10] There is a discrepancy regarding the inclusion/exclusion of patients based on vein size among previous research. Sincos et al.[6] included patients with a vein diameter of 5 to 12 mm, whereas Subramonia and Lees[7] included those with 3- to 12-mm veins. Helmy ElKaffas et al.[8] did not apply a minimal threshold for the vein diameter, and their maximal threshold was 18 mm. We were able to successfully treat patients with relatively large veins using RFA, therefore believe that large GSV diameter should not discourage surgeons from utilizing this minimally invasive technique for their patients. In fact, Shaikadov et al.[9] demonstrated improved outcomes after RFA compared to HLS in patients with a GSV diameter of ≥14 mm.

Our analysis showed that the majority of patients in the RFA group underwent above-knee treatment, unlike the HLS group, in which the majority underwent complete stripping. We observed similar rates of paresthesia in both groups. There is conflicting evidence from previous research regarding treatment length and nerve injury.[11-15] A recent single-center, retrospective analysis by Liu et al.[11] revealed better outcomes, including less nerve injury, less operative bleeding, reduced operative time, and shorter hospitalization in patients treated with a modified above-knee technique versus those treated by complete stripping. On the contrary, Uncu[12] reported acceptable nerve injury rates in his single-surgeon experience of 102 procedures. There is also ongoing debate on whether proximal or distal stripping is superior to each other with regards to nerve injury.[13-15] Below-knee treatment with endovenous thermal ablation techniques has been mainly avoided due to close anatomical relationship of sensory nerves with superficial veins in the crus. Nerve injury during endovenous thermal ablation treatment of the small saphenous vein is well-studied, unlike during below-knee GSV ablation.[16,17] However, there are recent reports with successful thermal ablation treatment of whole-length or below-knee GSV insufficiency with acceptable nerve injury rates.[18,19] We performed below-knee RFA in patients with crural GSV insufficiency and did not observe nerve injury afterward. Further research is needed to assess safety of thermal venous ablation of below-knee superficial veins.

Groups were comparable in terms of complications, and our complication rates were similar to or lower than results of previous reports.[20-26] This result could have been altered depending on complication definitions. For example, ecchymosis or hematoma, adverse events that are expected to be more common after HLS, were not included in our analysis.

Other researchers reported shorter postintervention hospitalization durations after RFA compared to HLS, whereas length of hospital stay was similar between groups in our study.[6,8] This was most probably due to widespread use of spinal anesthesia in our cohort, which rendered patients to stay longer in the bed after procedures. Others mostly used local anesthesia during RFA, and spinal block or general anesthesia during HLS, therefore observed significantly shorter lengths of stay after RFA.[6,8] Unlike conventional surgery, endovenous ablation techniques can also be performed in outpatient settings.[23] When performed under local anesthesia in the office setting, RFA is associated with significantly reduced hospitalization rates and reduced costs compared to HLS performed in the operating theater.[27-29] Cost-effectiveness was out of the scope of our study. Future research should include this variable when comparing different treatment modalities for venous disease.

There are some limitations to this study. The follow-up duration was short; therefore, we were not able to analyze more robust outcome measures, such as long-term obliteration rates, long-term patient-reported outcomes, and long-term CEAP and VCSS scores. Cost-effectivity analysis could not be performed.

In conclusion, radiofrequency ablation is associated with significantly less postoperative pain and earlier return to daily activities compared to HLS in patients with symptomatic GSV insufficiency. Both procedures have high success and low complication rates in a 30-day follow-up.

Ethics Committee Approval: The study protocol was approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (date: 24.04.2019; no: 2019/514/152/4). 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: Idea/concept, design, control/supervision, data collection and/or processing, analysis and/or interpretation, literatüre review, writing the article, critical review, references and funding, materials, approval of the final version: A.C.T.; Idea/concept, design, critical review, approval of the final version: A.O.

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Is del Nido cardioplegia safe in isolated coronary bypass surgery? It may be possible with this method

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ABSTRACT

Objectives: This study aimed to share the early results of the del Nido (DN) solution used with a different method in patients who underwent isolated coronary bypass.

Patients and methods: The retrospective study included 150 patients (123 males, 27 females; mean age: 59.8±9.7 years; range, 38 to 84 years) who underwent isolated coronary bypass operation between January 2020 and May 2022. The DN solution was applied differently from the practice in the literature. Seventy-five percent of the dose calculated according to the body weight of the patients was administered at the first moment. The remaining amount was continued to be given through the saphenous veins as distal anastomoses were made. When the cross-clamp was lifted, all grafts were tied to the aorta cannula, and the coronary vascular bed was cleared. Follow-up of patients was done routinely.

Results: The mean preoperative ejection fraction was 49.9±5.6, and the mean postoperative ejection fraction value was 50.3±5.0 (p=0.079). A statistically significant difference was found between the preoperative troponin level and the postoperative troponin level at 6 h (p<0.001). However, there was no significant difference between the postoperative 6 h and the postoperative 24 h. Spontaneous rhythm occurred at the termination of cardiopulmonary bypass in most of the patients (97%). No permanent pacing was required in any patient. An intra-aortic balloon pump was used in nine patients, and extracorporeal membrane oxygenation was used in two patients. Two patients died in the early period.

Conclusion: The use of DN with this method seems to be a reliable alternative to eliminate hesitations in isolated coronary bypass surgery.

Keywords: Cardioplegia, coronary artery bypass surgery, del Nido.

Myocardial protection is crucial in cardiac surgery. Ideal cardiac arrest ensures the immobility of the heart and provides energy to protect the myocardium. There have been attempts to achieve diastolic arrest by administering cardioplegia directly to the coronary vessels. Different suggestions have been made for this purpose.[1,2] Studies were carried out in terms of content, temperature, application method (antegrade or retrograde), and duration. Although del Nido (DN) cardioplegia was first used in pediatric cardiac surgery, studies have shown that it can also be used in adult cardiac surgery.[3,4]

The contents of DN cardioplegia solution are presented in Table 1. This solution differs from classic cardioplegia in that it contains lidocaine, which limits calcium entry into the cell and prolongs the duration of action.[5] It reduces the intracellular accumulation of harmful calcium ions, decreases the energy consumption rate, enables free radical clearance, and causes a major reduction in myocardial edema.[6] It is administered as a single dose. According to a study, the most important benefits include postoperative spontaneous rhythm, less need for defibrillation and inotropic support, and rapid improvement in troponin values.[7]

Studies showing positive results of DN use in adults have increased. However, it is still not widely used in adults. Based on previous studies, we aimed to share the early results of surgeries in which we used the DN solution.

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PATIENTS AND METHODS

The retrospective study was conducted with 150 patients (123 males, 27 females; mean age: 59.8±9.7 years; range, 38 to 84 years) at the Atatürk University Research Hospital between January 2020 and May 2022. At the beginning of 2020, the DN cardioplegia solution was started to be used in the surgeries of coronary artery patients in our clinic. Previously, cold blood cardioplegia was used. The only exclusion criterion was reoperations. The demographic characteristics of all patients, EuroSCORE II data, intraoperative data, postoperative follow-up data, drainage amounts, and postoperative ejection fractions were recorded. The preoperative and postoperative laboratory data were compared and analyzed retrospectively. The primary outcomes of the study were significantly increased troponin levels and decreased lower ejection fraction values, and the secondary endpoint was death.

Surgical procedure and method of cardioplegia delivery

All patients were operated with a median sternotomy. A left anterior thoracic artery (LITA) graft was used in all patients, except for two in whom LITA was dissected. The Trillium Affinity NT (Medtronic, Minneapolis, MN, USA) was used as the oxygenator, and the Terumo Advanced Perfusion System 1 (Terumo Cardiovascular, Ann Arbor, MI, USA) was used as the perfusion system. Standard cannulation was performed from the atrium and aorta in all patients, and the cardioplegia was delivered from the aortic root. In the first stage, 75% of the cardioplegia solution, calculated according to weight, was administered all at once. The remaining amount was continued to be applied at half the rate of the first application from the graft after each distal anastomosis. At the end of the distal anastomoses, the cardioplegia solution was set to run out. After the cross-clamp was lifted, the cardioplegia cannula was connected to the aortic cannula, and the cardioplegia solution was removed from the myocardium by continuously washing it with hot blood. The patient's body temperature was held at 32-34°C. After the cross-clamp was placed, a topical cold application was administered to the myocardium. The cardioplegia solution was delivered as described here: For a 70-kilogram adult patient, a 70×20=1,400 mL solution was prepared as the first dose. Of this amount, 75% (1,050 mL) was initially delivered. The remaining 350 mL was continuously applied from the grafts with a lower flow rate after each of the distal anastomoses was finished. The properties of the cardioplegia solution are presented in Table 1. Proximal anastomoses were performed with a side clamp. Neutralization with protamine was performed after decannulation.

Postoperative follow-up

In our clinic, hemodynamic or neurological follow-ups were performed in accordance with the routine procedure. Vital signs and laboratory values were recorded. Along with routine laboratory follow-ups, troponin I values were monitored in the first 24 h (at postoperative 6 and 24 h). The hemograms and electrolytes of all patients were monitored four times a day during the intensive care follow-up. Blood transfusions and electrolyte replacements were performed based on these results. The drains in the patients were removed if they collected less than 100 mL in the previous 12 h. Patients with stable hemodynamics were discharged from the intensive care unit. Patients who did not have any problems during follow-up were discharged.

Table 1
Contents of the del Nido cardioplegia solution

del Nido plegia solution (1000 mL* Izolex-S, Isolyte) pH: 7.4	%	mL
Potassium chloride	7.5 1 mEq/L	26
Magnesium sulphate	15	14
Sodium bicarbonate	8.4 1 mEq/L	13
Lidocaine	2	6.5
Mannitol	20	17
Blood		200

* After cardiopulmonary bypass, 200 cc of fluid is drained and the same amount of warm autologous blood is added.

Statistical analysis

The Number Cruncher Statistical System 2007 (NCSS LLC., Kaysville, UT, USA) was used for the statistical analysis. When evaluating the study data, descriptive statistical methods were used (mean, standard deviation, median, frequency, ratio, minimum, and maximum), and the distribution of the data was calculated using the Shapiro-Wilk test. The Friedman test was used for quantitative comparisons of three or more periods that did not show normal distributions, and the Wilcoxon test was used for two-term comparisons. Significance was evaluated at $p<0.01$ and $p<0.05$.

RESULTS

The patients' demographic characteristics, EuroSCORE II data, body mass index, and preoperative ejection fractions are presented in Table 2. The mean cross-clamp time was 49.2±16.1 min, and the mean cardiopulmonary bypass time was 100.2±26.6 min. The lowest operational temperature of the patients was 28°C, and the mean was 31.7±0.9°C. The mean number of grafted vessels was 3.1±0.8. All operational and postoperative follow-up data on the patients are given in Table 3. An intra-aortic balloon pump (IABP) was placed in nine of the patients due to chest pain and hemodynamic instability during the preoperative period. Intra-aortic balloon pump support was given to eight patients who did not have IABP in the preoperative period. The mean amount of cardioplegia solution used was 1,591.1±224.5 mL. Extracorporal membrane oxygenation (ECMO) support had to be given in addition to IABP at the termination of cardiopulmonary bypass in two patients. After the removal of the cross-clamp, it was observed that spontaneous rhythm occurred almost uniformly (n=147, 98%). Two of the other three arrhythmic patients were defibrillated because ventricular fibrillation developed. In the remaining patient, intraoperative temporal pacing was achieved. The pacing was disabled when a spontaneous rhythm occurred shortly thereafter. In the postoperative period, 21 patients developed atrial fibrillation. Sinus rhythms were achieved in all of these patients with medical intervention. No other dysrhythmias (supraventricular tachycardia or ventricular fibrillation) that caused hemodynamic effects or required interventions during postoperative rhythm follow-up were observed in any patient.

Table 2
Demographic data and preoperative data

Parameters	n	%	Mean±SD	Median	Min-Max
Age (year)			59.8±9.7	61	33-84
Sex					
Male	123	82			
Female	27	18			
Body mass index (kg/m^2)			27.95±3.35	27.75	20.8-38.6
Body surface area (m^2)			1.95±0.16	1.95	1.59-2.46
Hypertension	51	34.0			
Diabetes mellitus	48	32.0			
Cigarette	44	29.3			
Hyperlipidemia	40	26.7			
COPD	11	7.3			
Peripheral artery disease	5	3.3			
Chronic renal failure	4	2.7			
Cerebrovascular disease	3	2.0			
EuroSCORE II			1.07±0.43	1	0.45-2.69
Emergency operation	4	2.7			

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease.

Table 3
Intraoperative and postoperative data

Parameters	Mean±SD	Median	Min-Max
CPB time (min)	100.17±26.59	98	45-203
Cross clamp time (min)	49.18±16.07	45.5	20-119
Body temperature (°C)	31.65±0.9	32	28-34
Number of vessels (n)	3.11±0.82	3	1-5
Pleji solution amount (mL)	1591.07±224.48	1.580	1120-2320
CPB entry ACT value	129.29±15.53	130	74-165
CPB exit ACT value	135.33±12.32	137	98-191
CPB entry			
pH	7.32±0.06	7.32	7.16-7.51
pO_2	239.65±58.52	221.5	104-405
pCO_2	42.78±6.1	42.45	24.8-58.9
HCO_3	21.8±2.34	21.6	13.3-37.1
BE	3.45±2.09	3.35	0.1-13.6
Saturation	99.04±0.61	99	96.8-100
NaCl	137.47±2.9	138	125-149
KCL	4.52±0.69	4.6	2.4-6.7
Glucose	155.48±41.08	150	86-301
Ca	1.33±0.14	1.32	0.85-2.01
Lactate	1.85±0.94	1.7	0.3-7.8
Hgb	7.16±1.51	7.15	5.1-12.3
Htc	22.4±4.11	22.2	13.8-37
Cross clamp 10^{th} min			
pH	7.35±0.06	7.34	7.2-7.58
pO_2	187.51±46.58	185	73.4-310
pCO_2	38.8±6.64	38.6	25.4-70.2
HCO_3	20.64±1.96	20.4	14.3-27.9
BE	4.16±1.89	4.1	0.1-12
Saturation	98.84±1.13	99.05	90.4-100
NaCl	138.43±2.64	139	131-151
KCL	4.64±0.68	4.7	3-6.5
Glucose	196.38±45.22	195	99-329
Ca	1.27±0.08	1.27	1-1.46
Lactate	2.69±1.7	2.4	0.9-18
Hgb	7.76±1.09	7.7	5.8-12.3
Htc	23.94±3.64	23.9	4.3-37.9
CPB exit			
pH	7.36±0.06	7.35	7.13-7.56
pO_2	189.17±36.1	195	22.4-295
pCO_2	38.37±5	38.7	23.1-52.7
HCO_3	20.99±1.58	20.9	15.1-24.9
BE	3.72±1.52	3.5	0.1-9.4
Saturation	99.03±0.72	99.2	96.3-100
NaCl	139.39±1.83	140	130-145
KCL	4.55±0.48	4.65	3-6.1
Glucose	186.28±43.26	187.5	115-351
Ca	1.30±0.06	1.31	1-1.51
Lactate	2.76±1.22	2.55	1.1-8.8
Hgb	7.93±1	7.9	5.6-11.1
Htc	24.57±2.98	24.1	17.7-39.0
Extubation time (h)	6.07±1.52	6.12	4.2-20.7
ICU stay time (h)	48.63±10.268	49.2	36-142
Hospital stay time (day)	5.94±1.20	6.1	5-12

SD: Standard deviation; CPB: Cardiopulmonary bypass; ACT: Activated clotting time; BE: Base excess; NaCl: Sodium chloride; KCL: Potassium chloride; Ca: Calcium; ICU: Intensive care unit

Table 4
Preoperative and postoperative laboratory data

	Preoperative			Postoperative 6th hour			Postoperative 24th hours			
Parameters	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
BUN (mg/dL)	21.42±7.05	20.75	9.3-56.4				24.58±7.02	23.1	14.4-68.5	0.001*
Creatine (mg/dL)	0.9±0.23	0.87	0.42-2.31				1.01±0.25	0.95	0.69-2.56	0.001*
Hgb (g/dL)	14.53±1.92	14.7	9.5-20				8.7±0.85	8.6	6.4-12.1	
Hct (%)	42.77±5.24	43.1	27.9-59.6				26.09±2.19	6.1	18.8-32.7	
WBC (K/mm^3)	8.37±1.28	8.2	5.5-13.4				14.86±2.69	14.6	8.7-26.9	
PLT (K/mm^3)	262.78±70.14	258.5	102-605				176.28±36.3	171	88-295	
NaCl (mmol/L)	137.85±3.52	138.5	123-158				141.23±5.29	140	126-159	0.175
KCL (mEq/L)	4.21±0.4	4.2	3-5.6				4.29±0.4	4.2	2.7-5.1	0.119
Ca (mg/dL)	9.22±0.72	9.1	7.8-11.7				8.59±0.5	8.65	7.6-10.8	0.001*
CK (U/L)	87.81±56.55	71	13-337				75.79±38.66	68	15-285	0.195
CK-MB (U/L)	34.77±21.8	26	11-149				36.45±19.61	31.5	4-141	0.273
LDH (U/L)	263.31±31.7	261	170-404				257.74±22.8	256	195-329	0.063
Troponin I (ng/L)	76.42±106.57	28.6	0.9-763.5	731.04±374	662.85	112.3-2476.9	444.35±329.32	412.3	12.3-2727.5	0.001**
	Preoperative			Postoperative						
EF (%)	49.86±5.63	50	30-60	50.33±5.00	50	35-60				0.079

SD: Standard deviation; BUN: Blood urea nitrogen; Hgb: Hemoglobin; Hct: Hematocrit; WBC: White blood cell; PLT: Platelet; NaCl: Sodium chloride; KCL: Potassium chloride; Ca: Calcium; CK: Creatine kinase; LDH: Lactate dehydrogenase; EF: Ejection fraction; * Wilcoxon testi; ** Friedman testi.

Table 5
Postoperative complications

Complications	n	%
Atrial fibrillation	21	14
Bleeding revision	5	3.33
Pneumothorax	3	2
Cerebrovascular event (major)	1	0.66
Intra-aortic balloon pump	8	5.33
Extracorporal membrane oxygenation	2	1.33
Exitus*	2	1.33

* One patient died due to postoperative COVID-19.

The mean preoperative ejection fraction of the patients was 49.9±5.6, while the postoperative early-period values were 50.3±5.0. The pre- and postoperative values of troponin I, creatine kinase, creatine phosphokinase, and lactate dehydrogenase are given in Table 4. There were no significant changes from preoperative to postoperative creatine kinase, creatine phosphokinase, or lactate dehydrogenase values. Although troponin I values increased at postoperative 6 h relative to preoperative values, there was no significant difference between the values at the 6 and 24 h.

The mean duration of extubation was 6.1±1.5 h, hospital stay was 5.9±1.2 days, and intensive care follow-up time was 48.6±10.3 h. Important complications (such as renal failure, cerebrovascular accident, severe bleeding, and revision) encountered in postoperative follow-up are given in Table 5.

DISCUSSION

Coronary bypass surgery is the most common form of cardiac surgery. Myocardial protection of the heart during the operation is critical. There is no consensus on the method and content of cardioplegia used for this protection.[6] Reducing cross-clamp and cardiopulmonary bypass times is another important issue in cardiac surgery.[8] Since there is not much variation in the surgical procedure, efforts are continuing to reduce this time through cardioplegia support. Short cross-clamp and cardiopulmonary bypass time (44.2±14.1 min) observed in our study is consistent with the literature.[6] This reduction seems to be a significant contribution to an important issue in cardiac surgery. Although this was not the main point of our study, it is clear that single-dose administration contributes to the reduction of cross-clamp and cardiopulmonary bypass times. It would not be wrong to think that exposure to the unwanted side effects of the heart-lung machine will be decreased accordingly.

There are significant concerns about the use of DN cardioplegia in coronary artery disease, particularly in patients with multiple vessels.[9] Although an effective solution has been provided by administering retrograde cardioplegia to patients who are given conventional blood cardioplegia, there may be confusion in this regard since DN cardioplegia is applied all at once and antegrade. Another important benefit of not requiring retrograde cardioplegia is preventing complications, such as coronary sinus injury or bleeding from the entrance in the atrium. As suggested by our study, appropriate cardiac arrest can be induced with adequate myocardial protection without the need for retrograde cardioplegia. In the application of DN cardioplegia to multivessel patients in our clinic, after the first dose antegrade, one-fourth of the next dose was given from the anastomotic grafts (Figure 1). Thus, the distribution of cardioplegia solution to the whole heart was facilitated. We believe that this contributed to myocardial protection. There is convincing evidence that the DN cardioplegia solution provides strong myocardial protection.[7,10] In a study by Zeng et al.,[11] intermittent washing of metabolites and reoxygenation of blood were demonstrated as an advantage of cold blood cardioplegia. Regarding our method, we

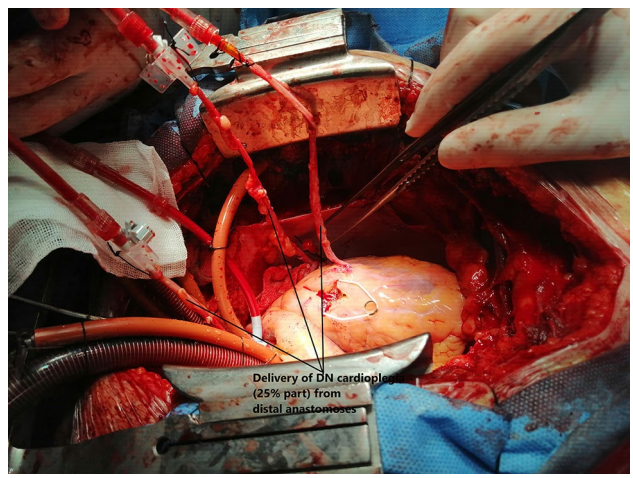

Figure 1. Intraoperative view of the cardioplegia solution being administered from saphenous vein grafts.

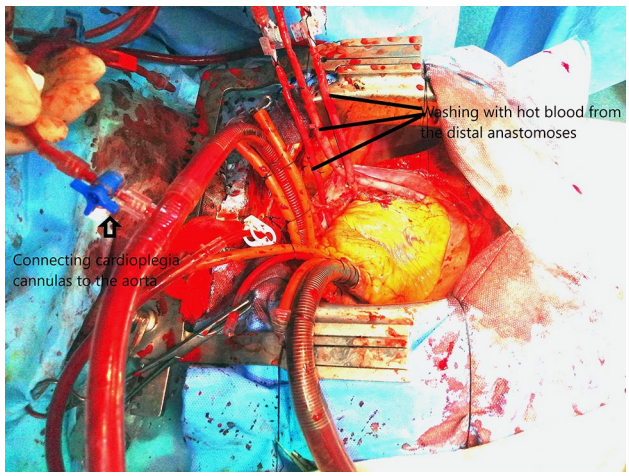

Figure 2. Image demonstrates the connecting of the cardioplegia cannulas to the aortic cannula after the cross-clamp is lifted.

believe that the continuous low dose of cardioplegia solution from the saphenous veins and, ultimately, the cleaning of the entire coronary vascular bed with warm blood from the aorta contributes to the removal of all metabolites, ensuring better protection of the myocardium (Figure 2).

The DN solution was developed to protect immature myocardium against reperfusion injury. However, it has been shown that it also provides functional improvements in elderly hearts.[12] Inspired by these studies, we have used the DN cardioplegia solution in our clinic for the last two years. Although no significant difference was observed in postoperative ejection fraction data in our study, the changes in troponin I values in postoperative follow-up are in accordance with most of the literature. Despite partial elevations, troponin I remained at acceptable levels after coronary artery bypass surgery. It would not be wrong to characterize the preservation of cardiac functions in terms of ejection fraction and troponin I levels. In contrast with this view, some studies have found that troponin I values were not low in groups given DN cardioplegia.[13] Although the main goal of our study was to properly protect cardiac functions through a new application of DN cardioplegia, the need for ventricular defibrillation and temporary pacemakers to address intraoperative arrhythmias was found to be reduced. The rate of spontaneous rhythm was noted to be higher. Since there was no control group in our study, the observational data were compared with the literature.[14] Considering that there were no differences in the intraoperative body temperatures, blood gas data, or electrolyte data of the patients, we believe this finding was an effect of the cardioplegic solution being strengthened. We think that delivering the blood from the aorta to the myocardium through saphenous vein grafts and completely cleaning the cardioplegia solution also contributed to this effect. Many studies have reported a significant decrease in ventricular fibrillation rates after DN use.[8,15] With less need for defibrillation, the possibility of subepicardial necrosis, which may occur through direct contact with the epicardium, is also reduced-contributing, in turn, to a reduction in myocardial damage.[16] Moreover, the components of DN are known to contribute to protection. Due to its hyperosmotic properties, mannitol is effective in clearing out free radicals and reducing edema.[17] Lidocaine acts as a depolarizing agent by inhibiting sodium channels and reducing calcium and sodium entry into cells.[18] Another important component in DN cardioplegia is magnesium. When used as an electrolyte, magnesium has been proven to increase myocardial recovery by blocking calcium channels.[19]

One of the challenges in cardiac surgery is the low cardiac output state. Mechanical support devices (IABP or ECMO) may be needed in patients who have difficulty weaning from a cardiopulmonary bypass and who develop low cardiac output state. The need for IABP ranges from 7 to 17% in different studies.[20,21] The fact that this rate was 6% in our study is seen as a positive outcome. In our study, the need for ECMO support in only two patients (patients with a 35% ejection fraction) was also interpreted positively.

When analyzing arrhythmias in our study, positive effects of the ingredients of the DN (mannitol, lidocaine, and magnesium) were observed. The main benefits were the formation of spontaneous rhythms and reduction in the duration and frequency of arrhythmias, such as atrial fibrillation and ventricular tachycardia. In our study, it was not possible to analyze all the etiological factors that may have caused these rhythm disorders one by one. However, the fact that the frequency of atrial fibrillation in the literature is 45 to 65% suggests that cardioplegia solution is effective at a lower frequency.[20,22] Of course, the findings on this subject will become stronger as studies are conducted with larger prospective patient populations. Another positive finding was that no significant ventricular arrhythmia was experienced in the early postoperative

period by any of the patients treated with DN. As in many studies, no differences were observed in the postoperative follow-up parameters (intubation time, major complications, or discharge time).[23,24] It was observed that observational intensive care follow-up times were shorter compared to our other patients who underwent conventional cardioplegia. We believe that the decreased postoperative arrhythmia contributed to this outcome. Waiting for patients to recover from arrhythmia before being removed from the ICU prolongs this period. No significant difference was observed in terms of the amount of drainage, the number of blood transfusions, the number of patients using inotropic support, or the laboratory data in the postoperative period, which reflects and supports findings that this cardioplegia solution can be used safely in isolated coronary artery bypass grafting.

One of the features of the content of the DN is a lack of glucose, which decreases the need for intraoperative insulin administration. Mick et al.[6] found that glucose levels were lower following the use of DN, and therefore, less insulin was required. In our study, we observed that intraoperative glucose control was easier with low glucose levels.

Although the use of DN cardioplegia for isolated coronary artery bypass grafting was not recommended in a study conducted at the Cleveland Clinic in 2014,[3] more reassuring findings have been reached in other studies.[15,25] Due to the lack of studies with prospective large patient numbers, concerns about this issue cannot be eliminated completely. However, as shown in many studies, DN cardioplegia has become increasingly preferred due to the shortened clamping and operation time and the possibility of performing cardioplegia all at once. In a large-scale study, Guajardo Salinas et al.[15] showed that DN cardioplegia application provides a significant economic advantage as well as other clinical benefits. We found that DN could be used safely in all patients undergoing isolated coronary bypass by following the method presented in our study.

The main limitation of this study is that since a novel application of DN cardioplegia was employed in the study, it could not be compared with the classical DN application. The data were compared instead with the literature. Additionally, only the ejection fraction and troponin I levels were taken as markers of myocardial protection. This restriction prevented a strong assessment from being made for analysis.

In conclusion, although DN cardioplegia solution is more common in pediatric cardiac surgery, it is increasingly used in adult cardiac surgery. However, there are still concerns about its use in isolated coronary bypass surgery. We believe that the method we followed together with a single-dose application will help address these reservations. Studies with more patients are needed for stronger interpretations.

Ethics Committee Approval: The study protocol was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (date: 04.15.2021, no: 3/48). 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: Idea/concept, design, literature review, writing the article: F.B.; Data collection and/or processing: Y.K.; Control/supervision, analysis and/or interpretation, final approval of the manuscript: B.E.; Analysis and/or interpretation, final approval of the manuscript: M.Ü., K.T.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Rotational atherectomy treatment before drug-eluting stent implantation in severe calcific coronary lesion

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ABSTRACT

Rotational atherectomy can effectively destroy calcified plaques and facilitate stent insertion and expansion in many cases. In this article, we present a successful application of rotational atherectomy with rotablator and drug-eluting stent implantation treatment in a 43-year-old male patient with severe calcific stenosis in the right coronary artery that could not be dilated with a high-pressure balloon. During the follow-up, the patient did not have any complaints as long as he was hospitalized, and no recent adverse events, such as acute stent thrombosis and bleeding, were observed.

Keywords: Calcific coronary artery stenosis, drug-eluting stent implantation, rotational atherectomy.

Drug-eluting stents (DES) have significantly reduced restenosis rates in randomized clinical trials evaluating simple coronary artery lesions.[1,2] In a study of 216 patients who underwent primary percutaneous coronary intervention for ST elevation myocardial infarction (STEMI), DES implantation was performed in all patients, and normal coronary artery flow was achieved in 84.3% of the patients. In-hospital mortality and postprocedure ventricular arrhythmia rates were found to be low.[3] Drug-eluting stents also showed favorable results when implanted in complex lesions, but higher rates of major adverse cardiovascular events were observed in subgroups of patients with complex lesions (e.g., bifurcation lesions) compared to patients with simple coronary lesions.[4,5]

Heavily calcified lesions pose a particular challenge due to resistant plaque burden, which may result in failure of stent deployment or expansion. This may increase the possibility of stent thrombosis or restenosis. In addition, heavily calcified lesions may pose a particular threat to DES; both damage to the polymer/drug coating during vigorous propagation and insufficient diffusion into the subintima may contribute to the ineffectiveness of DES.[5,6]

Rotational atherectomy (RA) can effectively destroy calcified plaques and facilitate stent insertion and expansion in many cases. However, when used alone or combined with bare metal stents, the risk of late restenosis remains high.[7] Recently, some observational studies have suggested a favorable long-term outcome of RA followed by DES implantation.[8,9] Theoretically, RA and DES can act synergistically in complex lesions as RA can prevent damage to the stent, and DES can effectively suppress neointimal proliferation. Therefore, RA of heavily calcified lesions may increase the efficacy of DES.[6] We present a case of severe calcific stenosis of the right coronary artery (RCA) successfully treated with rotablation and DES implantation.

CASE REPORT

A 43-year-old male patient who underwent coronary angiography and stent implantation with a known diagnosis of coronary artery disease 10 years ago presented to our clinic. The patient had comorbid hypertension and hyperlipidemia. Coronary angiography was performed in another clinic due to complaints of chest pain and exertional dyspnea. Upon

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detection of a severe calcific obstructive lesion in the RCA, balloon dilatation was performed, but it was unsuccessful. The patient was admitted to our clinic for further examination and treatment.

The patient was using nebivolol/hydrochlorothiazide 5/12.5 mg, acetylsalicylic acid 100 mg, clopidogrel 75 mg, perindopril/amlodipine 10/5 mg, atorvastatin 10 mg, fenofibrate 250 mg. Electrocardiography showed a sinus rhythm and T wave negativity in the inferior leads. In echocardiography, left ventricular ejection fraction was 60%, right ventricular ejection fraction was normal, left ventricular end-diastolic diameter was 4.5 cm, and left ventricular end-systolic diameter was 3.0 cm, with mild mitral valve regurgitation. Laboratory findings revealed hemoglobin 12.7 g/dL, creatinine 0.73 mg/dL, and low-density lipoprotein cholesterol 86.8 mg/dL.

In coronary angiography, RCA proximal and distal lesions were passed with a floppy guide wire. Since the 2.0×15 mm balloon did not pass through the lesion, a microcatheter was advanced to the RCA. Subsequently, the responsible lesions were tried to be predilated with a 2.5×15 mm balloon, but RCA patency could not be achieved. Considering these findings, it was decided to continue with a rotablator. The rotablator guidewire was advanced through the microcatheter. The rotablator procedure was performed with a 1.75 mm rotablator burr. Then, the distal lesion was predilated with a 3.0×15 mm balloon. A 3.5×16 mm DES was implanted into the distal lesion, and a 4.0×16 mm DES was implanted into the proximal lesion. The junction of both stents was dilated with a stent balloon. Right coronary artery patency was achieved. The procedure was completed without complications. During the follow-up, the patient did not have any complaints during hospitalization, and no recent adverse events, such as acute stent thrombosis and bleeding, were observed. The patient was discharged in good health.

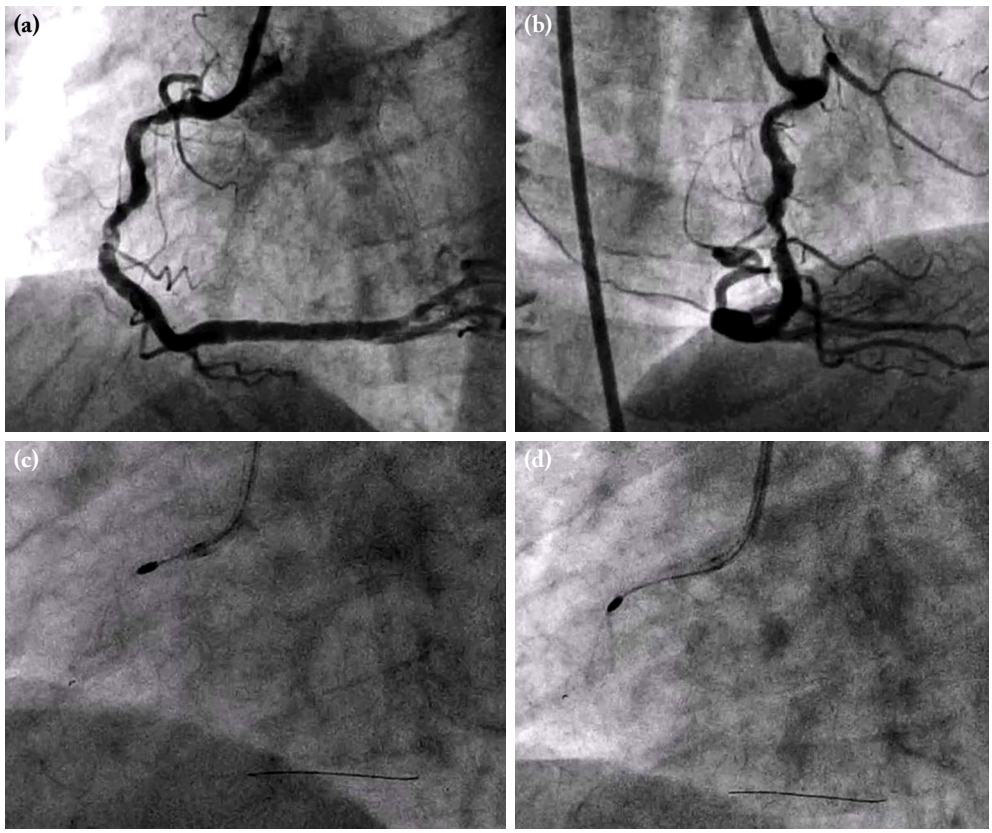

Figure 1. **(a, b)** Presence of severe and calcified lesions in the proximal and distal part of the RCA. **(c, d)** Application of rotational atherectomy for RCA stenosis.
RCA: Right coronary artery.

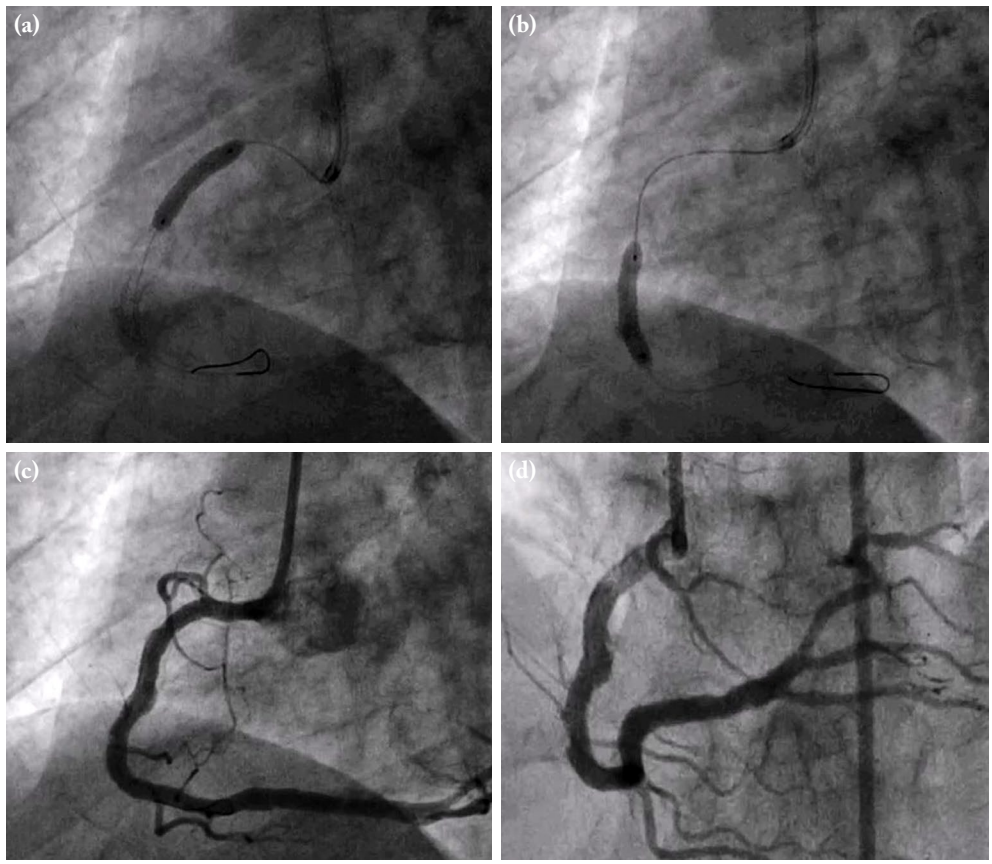

Figure 2. **(a)** Post-atherectomy drug-eluting stent implantation in the distal RCA calcific lesion. **(b)** Post-atherectomy drug-eluting stent implantation in the proximal RCA calcific lesion. **(c, d)** Angiography results.
RCA: Right coronary artery.

DISCUSSION

Significant coronary calcification is a major challenge and limitation for percutaneous coronary intervention, as it inhibits stent placement and expansion. This may be associated with poor stent expansion, target lesion restenosis, stent thrombosis, and myocardial infarction (MI).[10]

In the ROTAXUS (Rotational Atherectomy Before TAXUS Stent Treatment for Complex Native Coronary Artery Disease) study, 240 patients with complex calcified native coronary lesions were randomly assigned to two groups: RA followed by stenting (n=120) and stenting without RA (n=120, standard treatment group). Despite similar baseline characteristics, the strategy resulted in higher success in the rotablator group (92.5% *vs.* 83.3%, p=0.03), but restenosis (10.6% *vs.* 11.4%, p=0.71), target lesion revascularization (12.5% *vs.* 11.7%, p=0.84), stent thrombosis (0.8% *vs.* 0% p=1.0), and major adverse cardiovascular events (24.2% *vs.* 28.3%, p=0.46) were similar in both groups.[6]

Another recent study that included 154 patients showed comparable clinical results at 30-day and one-year follow-ups in those who did or did not undergo the RA procedure in acute MI.[11] This study demonstrated the safety and efficacy of RA in patients with acute or recent MI and reported that RA is a viable option due to a high procedural success rate. In the literature, RA has been successfully applied to calcific lesion in patients with acute STEMI and subacute MI.[12,13] In a prospective study of 76 patients with calcific superficial femoral artery lesions longer than 150 mm treated with drug-coated balloon angioplasty (DCB) alone or directional atherectomy

prior to DCB, primary coronary artery patency of the DCB and directional atherectomy with DCB groups at the 12-month follow-up was 66.6% and 82.6%, respectively ($p<0.05$).[14]

In light of the information we obtained in our case, the use of a rotablator before stent implantation in highly calcified coronary lesions reduces the risk of acute occlusion by providing a smoother lumen, provides increased lumen gain, reduces residual plaques, and reduces the risk of stent thrombosis through stent expansion and placement. Furthermore, RA is a proven procedure to modify the coronary lesions and facilitate stenting in severely calcified lesions when high-pressure balloon angioplasty alone cannot achieve dilation. In our case, the RCA lesion could not be opened despite high pressure with a balloon dilatation, and a combination of RA and DES was used. Rotational atherectomy and DES are complementary techniques in highly calcified lesions. Due to the inadequacy of data in the literature, new randomized clinical trials are needed to accurately evaluate these approaches.

In conclusion, the use of a rotablator before stent implantation in severely calcified coronary lesions provides a smoother lumen, reducing the risk of acute occlusion and providing comfortable expansion and placement of the stent.

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.

Author Contributions: Idea/concept, design, data collection, literature review, writing: M.K.; Control/supervision, critical review: N.B.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Giant pseudoaneurysm due to Dacron graft degeneration: A case report

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ABSTRACT

Knitted Dacron grafts are often preferred as they are easy to process, soft, and flexible; they also tend to expand due to their high porosity. Bleeding and pseudoaneurysm formation at the anastomotic site are common complications of vascular surgery, but nonanastomotic bleeding due to degeneration of Dacron graft's textile structure is rare. Here, we present a 70-year-old male diagnosed with a giant pseudoaneurysm that continues from the femoral artery to the popliteal artery formed due to the degeneration of the previous seven-year-old prosthetic graft. The pseudoaneurysm continued to be the source of arterial flow with its capsule, and the arterial flow into it was able to provide blood supply to the lower extremity without causing ischemia. The patient underwent surgery to excise the giant pseudoaneurysm and create a new bypass between the femoral and popliteal arteries. Today, the durability of prostheses is becoming increasingly important, and modifications in the manufacturing process have made Dacron grafts more resistant to cyclic pulsatile stretching and facilitated the adaptation of the prosthetic material to the host tissue. Despite all the remarkable innovations over the last 50 years, complications of prosthetic grafts can result in fatal bleeding. This situation emphasizes the importance of close follow-up and detailed clinical and radiological evaluation of patients.

Keywords: Dacron, graft degeneration, femoropopliteal bypass, peripheral artery disease, pseudoaneurysm.

In the surgical treatment of peripheral artery diseases, prosthetic graft materials are used when an autologous vein is unavailable. Although polyethylene terephthalate (Dacron) grafts are considered ideal arterial prosthetic grafts, some have been shown to have early or late complications.[1,2] Here, we present a case with a giant pseudoaneurysm formed along the former destroyed prosthetic graft, which continued to be the source of arterial flow throughout the popliteal artery (PA) in connection with the former femoropopliteal bypass graft operation. It was seen that the arterial flow in this giant pseudoaneurysm capsule could provide blood supply to the lower extremity without causing ischemia.

CASE REPORT

A 70-year-old male who underwent a left femoropopliteal Dacron bypass for peripheral artery disease approximately seven years earlier was evaluated with intermittent claudication, swelling, and pain in the left groin. The patient's medical history was limited due to the inadequacy of the medical records of earlier hospitals. In the physical examination, a pulsatile mass approximately 6×8 cm in size was present in the left inguinal region. Distal pulses of the left lower extremity were not palpable. Doppler ultrasonography revealed an 8×4 cm hematoma that spread into the muscle around the graft of the left superficial femoral artery (SFA). Examinations with angiography and computed tomography angiography were compatible with a short-necked aneurysm associated with the left SFA and a hematoma around the artery (Figure 1).

However, the surgical exploration of the graft site revealed a giant pseudoaneurysm caused by the degradation of the entire prosthesis. Since the pseudoaneurysm adhered to the venous structures posteriorly, only the fibrous capsule forming the anterior wall from the SFA to the PA could be excised. There was backflow from the distal portion of the PA. We observed that the previous graft material was Dacron and had begun to degenerate between native tissues but remained in pieces. There was no evidence

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of an isolated defect in the tissues around the graft. Femoropopliteal bypass surgery between SFA and PA-above knee with reversed *in situ* great saphenous vein was performed. The postoperative course was uneventful the year following the surgery, and the patient was free of symptoms (Figure 2).

DISCUSSION

Knitted Dacron grafts are easy to handle, soft, and pliable; however, they tend to dilate due to their high porosity. Knox[3] first reported structural deficiencies in prosthetic grafts in 1962. Bleeding or pseudoaneurysm formation at the anastomosis site is a common complication of Dacron grafts in vascular surgery. However, nonanastomotic bleeding connected to the degeneration of the textile structure of the graft and the formation of such a giant pseudoaneurysm starting from the femoral artery and continuing to the PA is rare in the literature.[4] The early detection of a Dacron rupture is tricky due to the unpredictability of the time between the clinical manifestation. In our case, we believe the diagnosis was delayed for this reason.

Manufacturing flaws, such as excessive heating during yarn texturization, crimping by thermal fixation, excessive stretching of yarns during knitting, chemical cleaning, and gamma or beta ray sterilization are possible causes for the loss of structural integrity

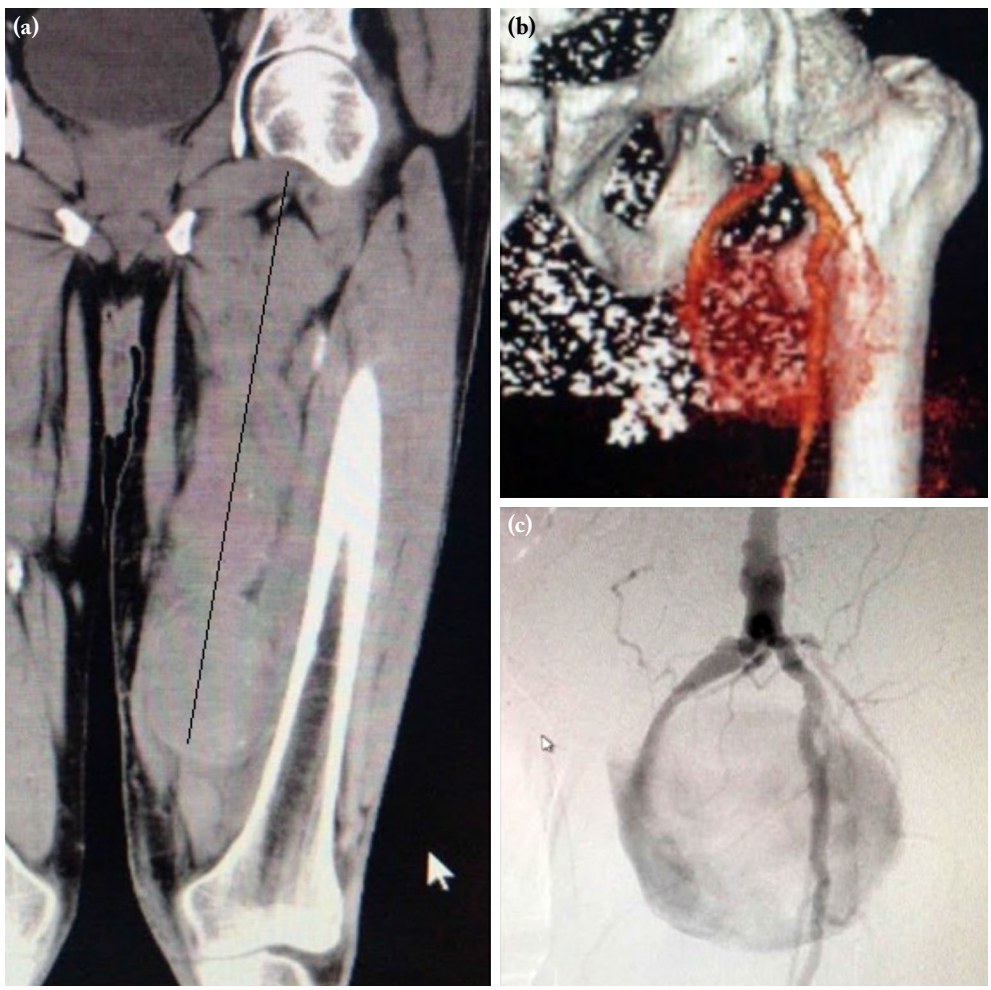

Figure 1. Radiologic imaging of the giant pseudoaneurysm is the source of arterial flow with its capsule and continues from the femoral artery to the popliteal artery. **(a)** The computed tomography angiography (coronal view); **(c)** Angiographic image; **(c)** digital subtraction angiography (DSA) image.

of a graft.[2,5] Generally, the graft fabrication process is standardized, computer-controlled, and extensive quality control measures are performed before the graft is marketed.[2] Intrinsic structural graft failure formations have been reported anywhere from 12 months to 19 years, with an estimated incidence of 0.5 to 3% in the earliest series (Figure 3).[1]

Some studies have reported giant cell reactions to fragmented Dacron fibers in the histological examination of the excised graft; however, they have not demonstrated an effective etiology or a predisposing factor.[1] In the histopathological examination, lymphocytic inflammatory infiltration was the only pathological finding involving inflammatory cells.

Graft infections in vascular surgery have the most severe complications, including anastomotic bleeding, sepsis, and death. The overall incidence of vascular graft infections is 1.5 to 2% in femoral grafts.[6] In our case, no infection was detected in both tissue and graft material.

In the present case, the late degeneration of the knitted Dacron fibers may have caused gradual stretching and focal disruption of the graft, resulting

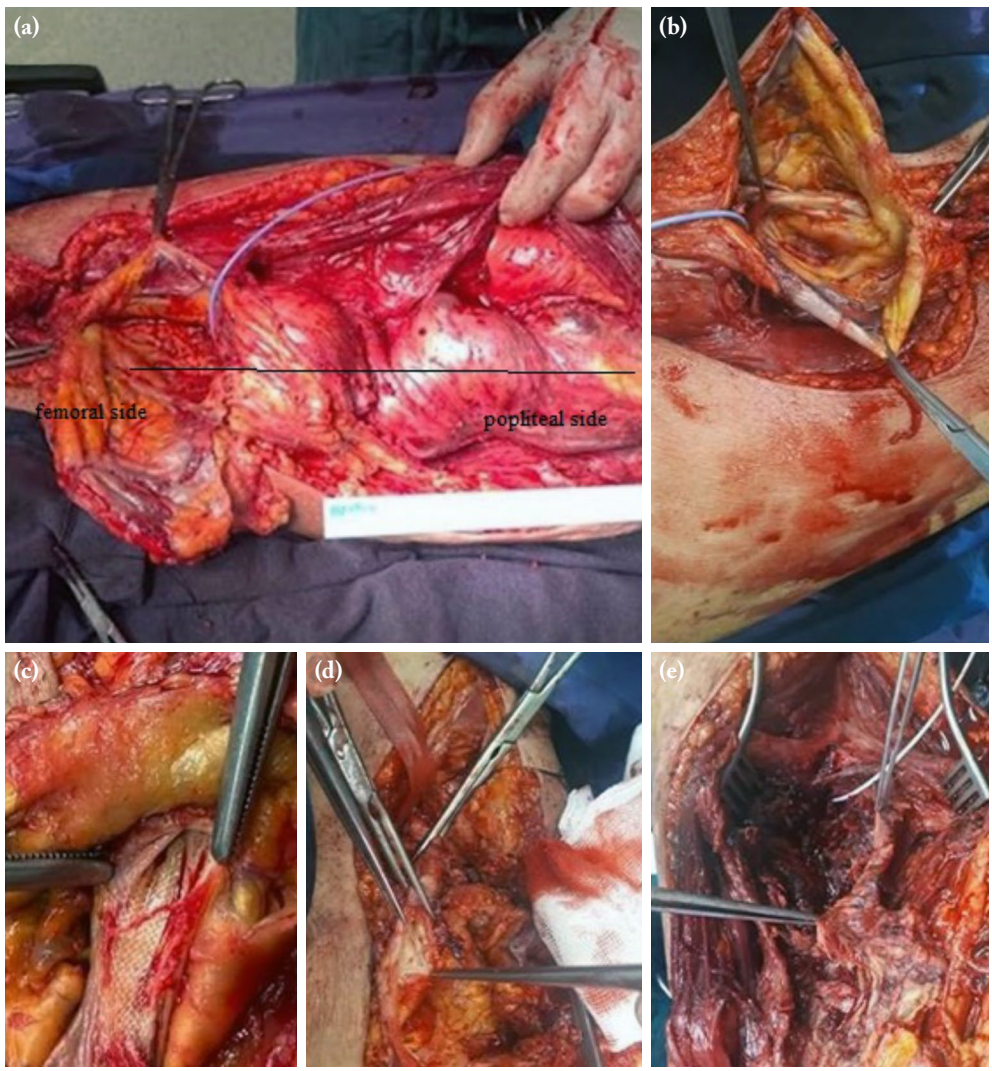

Figure 2. Surgical exploration of the giant pseudoaneurysm, and the former Dacron graft degeneration. **(a)** Fibrous capsule of the pseudoaneurysm (outside view), **(b)** Fibrous capsule of the pseudoaneurysm (inside view), **(c)** Degeneration of the Dacron graft, **(d, e)** Separation in Dacron fibrils.

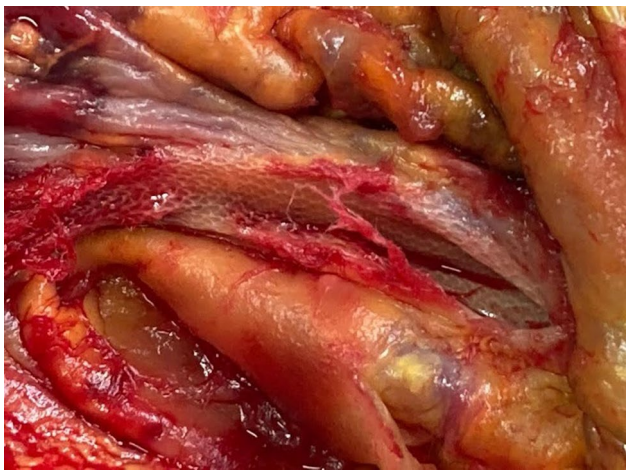

Figure 3. The degenerated Dacron graft with continued distal flow through the pseudoaneurysm capsule.

in a localized pseudoaneurysm that would subsequently enlarge.[7,8] Degradation may be related to many factors, such as designing the textile structure, fabrication flaws, modifications of the prosthesis during the manufacturing process or the surgery by inappropriate handling, unpadded clamps, or the surgeon's overstretching of the graft. There may have also been secondary physicochemical alterations due to chronic foreign body giant cell inflammatory reactions and mechanical fatigue caused by repeated bending and the constant systolic-diastolic arterial stresses.[4,9] Repetitive hydrodynamic microtraumas, as with pulsatile blood flow, cause progressive stretching and thinning of the yarn filaments due to cracking or gradual ruptures. The ends of these distorted, broken fibers appear tapered and frayed. Once this occurs, the load is transferred to the remaining neighboring filaments of the weave, resulting in torn fibers.[2] During the operation of this patient, we observed that the graft degenerated along its length, as if supporting the structural collapse.

Traditionally, aneurysms are treated by the excision of the disrupted graft and replacement with a new prosthetic graft.[7,8,10] In our case, we preferred an open surgical intervention for our patient's exploratory diagnosis and treatment.

This case study was not extensive. Graft degeneration should still be considered a late-term complication despite all the developments in the construction and inspection processes of Dacron grafts. No matter how much time has passed since the operation, complications related to grafts should be kept in mind.

In conclusion, the ideal vascular prosthetic conduit should be easily accessible, resistant to dilatation and infections, stable, biocompatible, and longstanding, with a durability superior to the patient's life expectancy. They should also provide and sustain a thromboresistant flow surface and have elastic properties that ensure a normal artery's patency, compliance, and flexibility.

Patient Consent for Publication: Written informed consent was obtained from both the patient and a legally authorized representative of the patient for their anonymized information published in this article.

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

Are we going to survive transplant during the coronavirus disease 2019 outbreak: A case report

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ABSTRACT

Coronavirus disease 2019 (COVID-19) creates a challenge on donor selection, posttransplant management, and immunosuppressive therapy. A question arises about continuing heart transplantation due to risk of immunosuppressive therapy, as well as exposure during hospitalization. After the identification of the first COVID-19 patient, our center conducted the management of selection and treatment of candidates and continued to perform cardiac transplantations. Herein, we present two cases who underwent successful heart transplantation after the determination of patient zero in Türkiye to highlight clinical implications by describing our clinical principle in the ethical knowledge of the International Society for Heart and Lung Transplantation COVID-19 task force statement regarding heart transplantation.

Keywords: COVID-19, heart transplantation, immunosuppressive therapy.

Coronavirus disease 2019 (COVID-19) creates a challenge in donor selection, posttransplant management, and immunosuppressive therapy. Underlying heart and respiratory disease, advanced age, and diabetes have been determined to play a crucial role in mortality, whereas patients having immunosuppressive therapy were also reported to be at risk.[1-3] Consequently, a question arises about continuing heart transplantation (HTx) due to risk of immunosuppressive therapy, as well as exposure during hospitalization.

CASE REPORT

The first patient was a 42-year-old female with ischemic cardiomyopathy waiting on the list since October 2018, and the patient had been in self-isolation since the beginning of the pandemic. The patient had a history of ventricular fibrillation resulting in acute myocardial infarction followed by cardiopulmonary resuscitation. At the time of hospital admission for surgery, the patient was clinically screened, and computed tomography (CT) imaging was evaluated. Finally, elective surgery was uneventfully performed on March 13 with an ischemic time of 150 min. The patient was moved out of the intensive care unit (ICU) on the second postoperative day and discharged home by the seventh postoperative day.

The second patient, a 32-year-old female, had been hospitalized since July 2019, waiting for a transplant. The patient underwent Fontan circulation for a univentricular heart with tricuspid atresia 24 years ago. The reverse transcriptase polymerase chain reaction test came negative, and the assessment of CT was normal. Urgent surgery was completed on March 20 with an ischemic time of 152 min. The patient was extubated after 16 h and discharged to the ward on Day four. Recovery was uneventful, and the patient was discharged home by Day 16.

During recovery, the mean white blood cell and neutrophil counts were, respectively, $15.3\pm5.3 \times 10^9$/L and 82±12.7% for the first patient and $15\pm8.4 \times 10^9$/L and 88±8.2% for the second patient. Demographic parameters prior to surgery are summarized in Table 1. Both donors were from out of Istanbul without history of epidemiological exposure or fever

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Table 1
Clinical characteristics of the patients

Characteristics	Patient 1	Patient 2
Age (year)	42	32
NYHA Class III-IV	+	+
Diagnosis	Ischemic	Congenital
Risk factors		
Diabetes	-	-
Hypertension	-	-
CVA/TIA	-	-
Arrhythmia	+	-
Renal failure	-	-
PAH	-	-
Hemodynamic		
EF	25	50
PAPm	27	9
PCWP	22	5
PVR	1.6	1.3
CI	1.89	1.8

NYHA: New York Heart Association; CVA: Cerebrovascular accident; TIA: Transient ischemic attack; PAH: Pulmonary arterial hypertension; EF: Ejection fraction; PAPm: Mean pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; CI: Cardiac index.

during hospitalization. Their CT scans were normal, and both donors were negative for COVID-19. In the light of current information and guidance from the International Society for Heart and Lung Transplantation regarding the COVID-19 pandemic, we did not make a change in induction and maintenance of immunosuppressive therapy.[4] For the initial phase of induction therapy, rabbit anti-thymocyte globulin was preoperatively used once due to its highly potent effects, which may cause cytokine release syndrome.[5] Glucocorticoids were first-line agents for induction and maintenance therapy. In our transplant program, we use a quadruple-drug maintenance regimen consisting of calcineurin inhibitor (cyclosporine), lowering with everolimus, an antiproliferative agent (mycophenolate mofetil), and a glucocorticoid (gradually rapid tapered) as a renal protective strategy. The mean postoperative cyclosporine and everolimus concentrations were 100.6±12.8 ng/mL and 4.3±1.08 ng/mL. The patients never had lymphopenia in the outpatient clinic. The examination of renal and liver function (urea, creatinine, serum glutamic-pyruvic transaminase, and serum glutamic-oxaloacetic transaminase) was normal. Surveillance biopsies were abolished against the risk of exposure in those that were not sensitized or had low risk for rejection. We preferred to use consecutive echocardiographic assessment for the detection of allograft rejection. Swab specimens were collected prior to discharge of patients and reported negative.

DISCUSSION

With the global outbreak of coronavirus, the organ transplant activity run into danger. Looking on the bright side, the experience from reviews of previous outbreaks on severe acute respiratory syndrome and Middle East respiratory syndrome suggests that immunosuppressed patients are not associated with higher risk of fatal complications compared to the general population.[2,6]

Our national pandemic coordination board, the Ministry of Public Health, released recommendations for limiting all planned surgery; therefore, we focused on more urgent patients, preserved the sources to more needy ones, and tried to prevent potential spread among healthcare workers and families of patients. However, the answer to whether transplant surgery should be performed or not is going to be diverse depending on the situation and epidemiology of the virus in your area. We emphasized the waitlist mortality risk and potential benefit for all listed hospitalized or at-home patients, identified selected patients that should not be postponed, and accepted good quality organs from proven donors to reduce long ICU stay and early graft dysfunction. Considering the epidemiological study from Ren et al.,[4] which showed that transplant patients taking appropriate precautions had low rate of COVID-19 infection, we evaluated our hospitalized patients and directed the medically stable ones to self-isolation at home. And it is just as well that we managed to perform transplantation in one of our self-isolated patients. We also considered alternatives such as left ventricular assist devices; nevertheless, it should not be utilized in elective patients to limit resources or avoid nosocomial infections.[5]

A recent study from Italy showed stable transplantation activity in contrast to our decreasing donor activity (75%) compared to the first quarter of the last year.[3] We are not there yet where every organ donor is routinely testing. Our protocol for the patients requiring HTx are as follows: *(i)* CT and

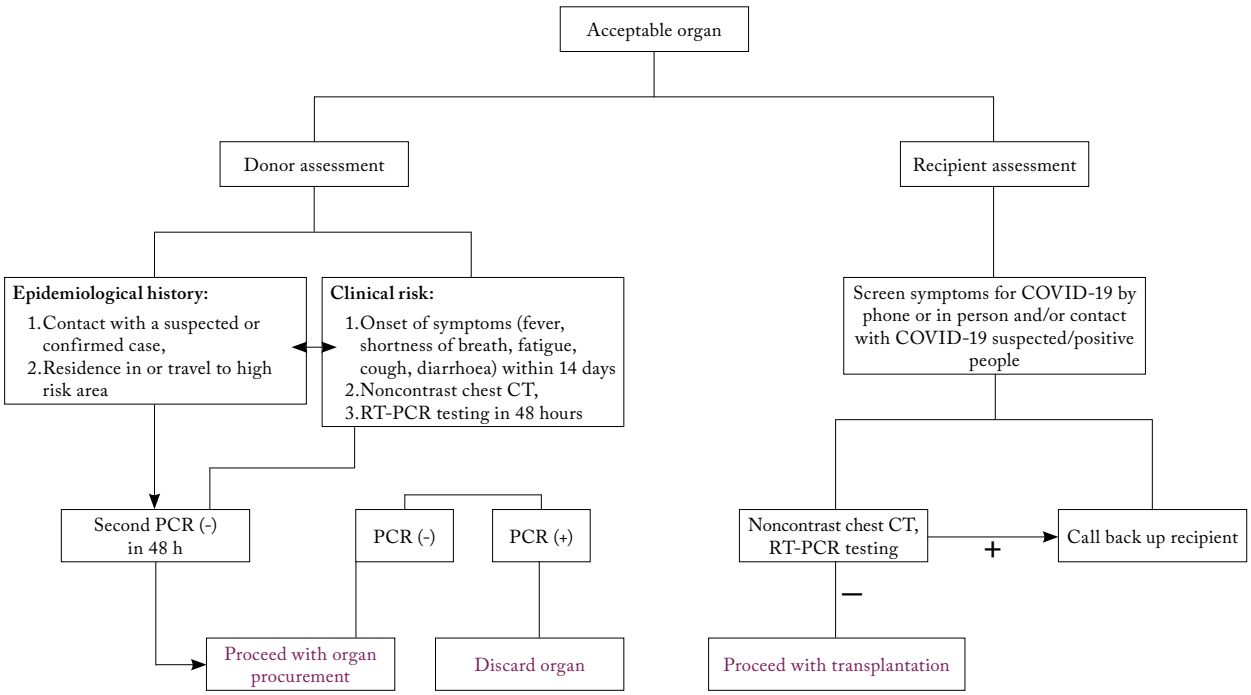

Figure 1. Our approach to heart transplantation during COVID-19.

CT: Computed tomography; RT-PCR: Reverse transcription polymerase chain reaction; PCR: Polymerase chain reaction; COVID-19: Coronavirus disease 2019.

rapid polymerase chain reaction are performed for already hospitalized patients; *(ii)* clinical evaluation and CT are performed for patients waiting at home; *(iii)* patients on the elective list must be privately transported and accompanied by one and the same relative all the time; *(iv)* recipients and relatives are retested and receive education for preventative precautions prior to discharge; *(v)* the donor must have no history of contact with a suspected or confirmed COVID-19 patient and of travelling abroad over the past 30 days; *(vi)* the donor must have no signs of pneumonia in CT or no positive nasopharyngeal swab result for COVID-19; *(vii)* the operation room, ICU, and the postoperative ward should be separated to avoid in-hospital disease transmission; *(viii)* shift schedules should be organized for related medical staff; *(ix)* immunosuppressive therapy should be continued unless otherwise indicated to reduce or discontinue doses. Our detailed approach to HTx during the global pandemic is described in Figure 1. Donors who are positive for both clinical and epidemiological screenings are considered high risk to be used for transplantation. If the donor tested positive for COVID-19, the organs should not be used for transplant. Computed tomography has been widely recommended to clarify patients with suspected COVID-19.[2] However, during the pandemic, the identification of COVID-19 pneumonia from pulmonary edema caused by heart failure was one of the major challenges for physicians. Most of the radiological features presented with COVID-19 can be seen in many systemic processes, and multiple underlying medical comorbidities, concomitant infections, and volume overload could influence the CT findings. Although the fatality rate is low (1-8.6%), patients with cardiac comorbidities present with a more severe outcome of COVID-19.[3]

In conclusion, we believe that patients having HTx are already used to social distancing and applying sanitization measures. Sharing knowledge and transparency with patients and other centers are important to come out with less damage through this pandemic.

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

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

Author Contributions: Resources, materials, data collection, writing, literature search: Ö.A.; Data collection, materials: M.Ö., Materials, literature search, review: M.A.; Supervision, review: K.K.

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Cardiovascular Surgery and Interventions

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Giant asymptomatic pulmonary herniation following minimally invasive mitral valve replacement

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ABSTRACT

Minimally invasive valve procedures have become the standard procedure for valvular surgery. Right thoracotomy is the preferred incision for mitral or tricuspid interventions. Complications regarding thoracotomy are almost always either overlooked or ignored. Pulmonary herniation is not that infrequent, but mostly asymptomatic or masked. Pulmonary herniation through thoracotomy incision is the most common presentation and is usually in a limited area. Herein, we present a 62-year-old female patient with giant pulmonary herniation that did not cause any respiratory issues following minimally invasive mitral valve surgery. No treatment was required for pulmonary herniation. She was only given full medical therapy for heart failure.

Keywords: Minimally invasive surgical procedures, pulmonary herniation, thoracotomy.

Minimally invasive cardiac surgery is a frequently preferred option in the last two decades for surgical valvular procedures, predominantly right thoracotomy approach for mitral or tricuspid pathologies.[1] The implemented advantages over applicability and durability of the procedure include lower pain and discomfort easing earlier return to normal life.[2] However, reported drawbacks often include recurrent valvular pathologies, and often incision-related complications are either overlooked or ignored and not reported. Pulmonary herniation is an incision-related complication following minimally invasive valvular procedures. Herein, we report a case of giant pulmonary herniation following right thoracotomy approach mitral valve replacement surgery that does not cause any respiratory issues.

CASE REPORT

A 62-year-old hospitalized female patient treated for heart failure was consulted with us for a visible lung herniation during respiration. The patient had a visible in-and-out movement of the respiratory wall due to inflated and deflated pulmonary tissue, and the herniated chest wall only consisted of skin and subcutaneous tissue (Figure 1a and Video 1). A mitral valve replacement surgery with the right thoracotomy approach was performed seven years ago in a different center. The postoperative course was eventful, with femoral access site nosocomial infection treated with vacuum-assisted therapy. The patient had a minor hernia that did not cause any respiratory symptoms located above the incision, which had gradually increased in size over the years.

Plain chest X-ray revealed complete 12 ribs on the right side (no ribs were excised or removed during surgery), and computed tomography scan documented a great area of herniation of the pulmonary tissue (Figure 1b).

The patient had a pacemaker implanted and advanced heart failure. The patient was left untreated for the hernia since it was asymptomatic, and the medical status of the patient would not allow a chest wall repair surgery under general anesthesia.

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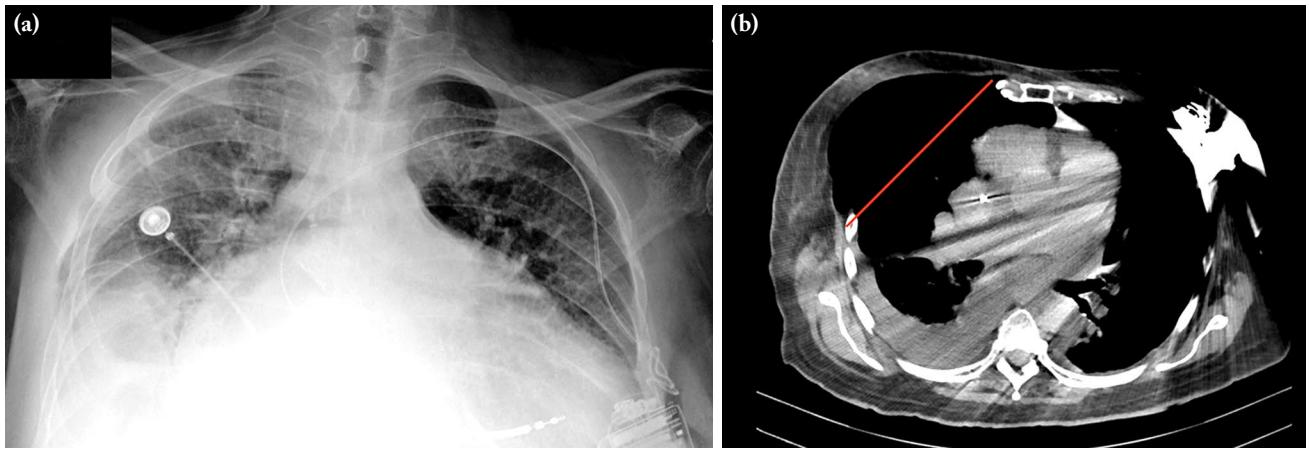
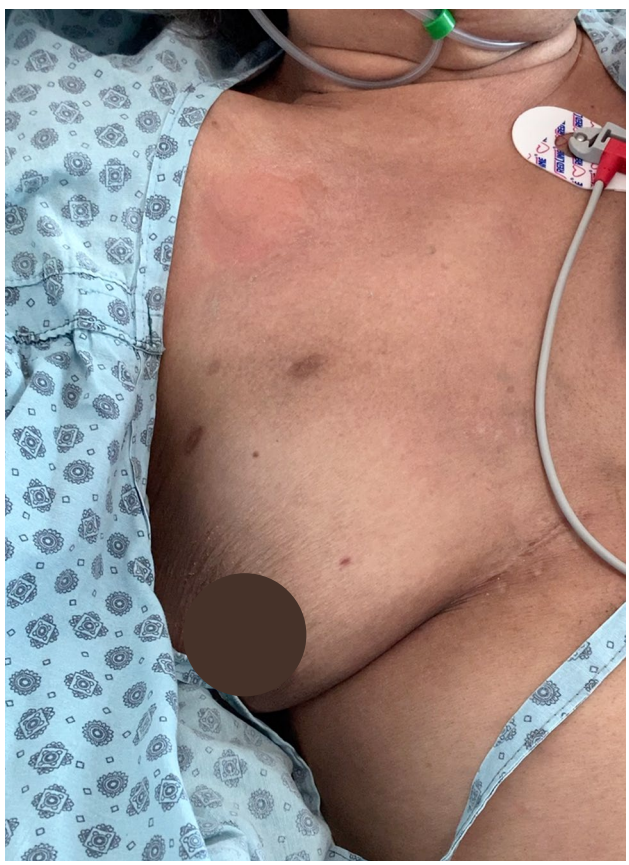


Figure 1. **(a)** Chest wall with complete 12 ribs on X-ray. **(b)** Computed tomography scan documenting a great area of herniated pulmonary tissue (red line).



Video 1. Respiratory pattern of the patient.

DISCUSSION

Pulmonary herniation is an infrequent diagnosis, which can be either congenital or acquired; the latter being traumatic, spontaneous, or pathologic. It can be occasionally encountered following thoracotomy. Herniation is usually visible in males in contrast to females since breast tissue masks the herniated tissue. Patients usually complain of pain during coughing. Unlike the patient presented here, patients may complain of a persistent cough, dyspnea, and haemoptysis.[3] Treatment is surgical with autologous graft chest wall reconstruction.[4] The pathology itself is not infrequent following surgical valvular procedures with the right thoracotomy approach but is mostly overlooked or ignored and consequently not reported.

A detailed report of 20 cases stated that pulmonary herniation was an infrequent entity and minor herniations were more common.[4] The patient we reported has a very large area of pulmonary herniation, but the pathology did not cause any respiratory problem. The chest wall was flail with only skin and subcutaneous tissue covering the lungs. The patient's dyspnea was caused by cardiac failure rather than pulmonary herniation.

In conclusion, it should be kept in mind that pulmonary herniation may occur following minimally invasive mitral valve surgery. Minor herniations are more frequent. The treatment varies depending upon patient's condition.

Patient Consent for Publication: A written informed consent was obtained from 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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Transaortic cardioscopic left ventricular thrombectomy

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ABSTRACT

Left ventricular thrombi are mostly seen after complicated myocardial infarction, endocarditis, and myocarditis. Left ventriculotomy is the most common approach for removing a left ventricular thrombus and treating an aneurysm. However, it may occur without a ventricular aneurysm. Myectomy may cause many cardiac complications for vulnerable myocardium. Herein, we describe the case of a 51-year-old male treated with the successfully transaortic cardioscopic approach for left ventricular thrombectomy with a mobile thrombus and no myocardial aneurysm.

Keywords: Cardiac aneurysm, endoscopic surgical procedure, myocarditis, thrombus.

Left ventricular (LV) thrombus is a frequent complication of myocardial infarction, dilated cardiomyopathy, and myocarditis.[1] Left ventriculotomy is the most common approach for removing thrombi and treating aneurysms. This approach carries risks such as ventricular dysfunction, cardiac arrhythmias, contractile dysfunction, and bleeding. If the thrombus is mobile and pedunculated and there is no LV aneurysm, left ventriculotomy may not be necessary. We describe a case of endoscopic transaortic LV thrombectomy without ventriculotomy.

SURGICAL TECHNIQUE

A 51-year-old male presented with complaints of exertional dyspnea, fatigue, and shortness of breath that persisted for five days. He had a history of diabetes mellitus and hypertension. He also had a history of coronavirus disease 2019 (COVID-19) a month ago. There were disseminated crackles on both lungs, abdominal respiration, and hypertension on physical examination. No heart murmurs were heard, heart rhythm was sinus rhythm. Polymerase chain reaction test for COVID-19 was negative. Troponin level was positive (31,766.4 μg/L). The patient was on amlodipine, ramipril, and hydrochlorothiazide, and he was not taking any antiaggregant or anticoagulant therapy before admission. Chest computed tomography scan revealed bilateral pleural effusion and severe pulmonary edema. He was admitted to the medical intensive care unit for further investigations and intense medical therapy. The patient developed a transient ischemic attack, which appeared as a loss of consciousness for 5 min on the third day of admission.

Two-dimensional echocardiography revealed a 35% ejection fraction, anteroapical dyskinesia, moderate to severe mitral valve regurgitation, moderate tricuspid regurgitation, and a 3.5×1.5 cm mobile pedunculated thrombus, which attached to the apical left ventricle (Figures 1a, b; Video 1). Coronary angiography demonstrated a 20% stenosis in the left main artery, 30% stenosis in the left anterior descending artery, and 20% stenosis in the obtuse margin artery and right coronary artery. The patient was prepared for urgent cardiac surgery due to a potential recurrent thromboembolization.

A median sternotomy was done under general anesthesia. Aorta-right atrial cannulation was performed after heparinization. Cardiopulmonary bypass (CPB) was established. A cross clamp was placed on the aorta and antegrade blood cardioplegia

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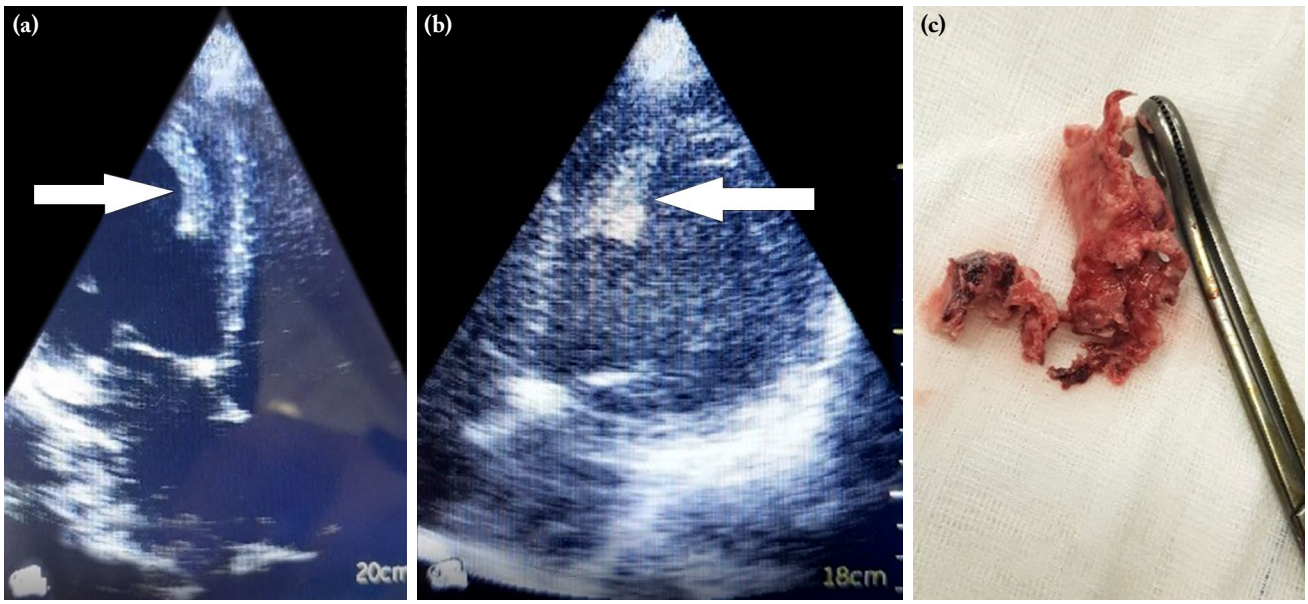
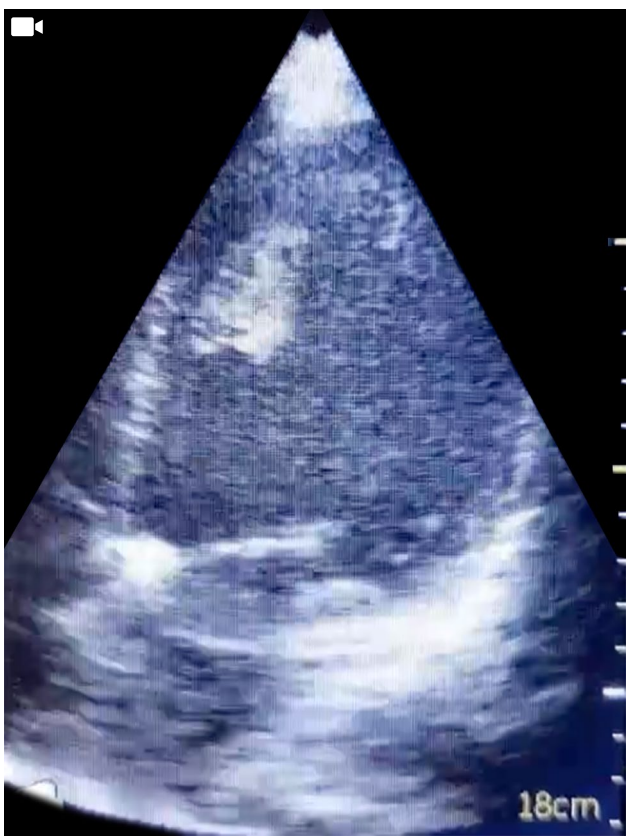


Figure 1. **(a, b)** Two-dimensional transthoracic echocardiographic images of the LV thrombus (White arrows). **(c)** Thrombus material extracted by transaortic cardioscopy.



Video 1. Transthoracic echocardiographic view of the mobile left ventricular thrombus.

was delivered to arrest the heart. There was no LV aneurysm on direct cardiac examination. A left atriotomy was done, and the LV cavity was checked through the mitral valve. There was a fresh thrombus attached to the LV apex. It was hard to remove the thrombus via the left atrial approach due to the mitral chordal engagement.

A transverse aortotomy was made in the ascending aorta. Aortic leaflets were retracted, and the LV cavity was examined. A 3.5×2×2 cm thrombus was removed under direct vision (Figure 1c). It was hard to fully observe the LV cavity for checking any residual thrombus. An endoscopic camera was advanced to the left ventricle through the aortotomy incision. Another 1×1×1 cm thrombus was removed from the LV apex. The LV cavity was checked by an endoscopic camera. There was no more thrombus in the left ventricle. The cavity was irrigated by saline, and the aortotomy was closed. The mitral valve was examined. There was mitral annular dilatation and partial posterior leaflet prolapsing. Mitral valvuloplasty and ring annuloplasty was done by a 30 mm semirigid ring device. Intraoperative transesophageal echocardiogram demonstrated no intracardiac residual mass or thrombi and mild mitral regurgitation. Dopamine, noradrenaline, and

intra-aortic balloon support were established during weaning from CPB circulation.

The postoperative course was stable. The patient was extubated after 7 h. The intra-aortic balloon was removed on the second day, and the patient was transferred to the ward on the third day and discharged on the seventh day after the surgery. Oral anticoagulant (warfarin) therapy was maintained for six months. His physical condition was good (New York Heart Association Class 1), the ejection fraction was 55-60%, there was mild mitral regurgitation, and no cardiac thrombi were observed on follow-up echocardiograms.

DISCUSSION

Left ventricular thrombi is mostly seen in patients with complicated myocardial infarction. Cardiac surgery morbidity and mortality risk increases in patients who have had COVID-19 infection in the perioperative period. Postponing the cardiac surgery for COVID-19-infected patients was advised if possible.[2] Our patient had a history COVID-19 a month before surgery, and the real-time polymerase chain reaction was negative preoperatively.

The presence of LV thrombi is associated with a risk of systemic embolization. The results of conservative treatment for mobile and pedunculated LV thrombi are poor compared to surgical treatment.[3] The mobility of an LV thrombus and history of cerebral embolism were strong indications for urgent cardiac surgery.

Surgical treatment is mostly performed by LV aneurysmectomy if there is an aneurysm. However, if there is no LV aneurysm, ventriculotomy may cause severe complications, such as severe arrhythmias, depressed myocardial contractility, and bleeding. A lot of new intracardiac thrombi case reports related to COVID-19 infection were recently published,[4-6] and it was remarkable that most of these cases did not form an LV aneurysm.[7]

In our case, the patient had no LV aneurysm but a mobile pedunculated thrombus in the LV apex and moderate to severe mitral valve regurgitation with noncritic coronary artery stenosis. Video-assisted cardioscopy was previously reported in a cardiac tumor and a thrombus excision.[8,9]

Left atriotomy could be a choice for the LV approach, but mitral chordal structure and fragility of the thrombus may not allow to reach and remove the thrombus safely. Cardioscopy could be done through the left atriotomy as a transmitral approach. Unfortunately, our camera body was rigid and straight, the chest was deep, and the handle of the camera was not flexible. Transaortic approach is another choice. Therefore, we reached the inside of the left ventricle by the gentle retraction of aortic leaflets, and an endoscopic camera facilitated a view of the deep part of the LV cavity. All thrombus parts were removed safely, and the LV cavity was visualized by an endoscopic camera and irrigated by saline. Mitral ring annuloplasty was performed, and the operation was completed without any complications.

In conclusion, transaortic cardioscopy facilitates LV thrombectomy and avoids ventriculotomy. This is practical for removing a mobile or pedunculated LV thrombus in the absence of an LV aneurysm.

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

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

Author Contributions: Idea, concet, design, control/supervision, data collection and processing, analysis, literature review, writing the article, review, references, materials: M.B.A.; Idea, data collection, literature review: B.U.

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