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Long-term follow-up of infective endocarditis: Rates of reinfection, mortality, and predictors of outcome

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ABSTRACT

Objective: Infective endocarditis (IE) is a severe condition characterized by high mortality rates. We aimed to assess reinfection and mortality rates in IE patients at a tertiary referral center during long-term follow-up.

Patients and Methods: We retrospectively analyzed 204 patients meeting modified Duke criteria for definite IE between 2009 and 2019. Early reinfection was defined as occurrence within 6 months, and late reinfection was defined as occurrence 6 months after the initial diagnosis.

Results: Mean follow-up duration was 40.3 ± 26.4 months. Valve surgery was performed in 125 patients (69.8%), while 54 (30.2%) received medical therapy alone. Early reinfection was
seen in 9 patients (5.1%), and late reinfection in 12 patients (6.7%). Staphylococci (41.9%), Streptococci (26.3%), and Enterococci (15.6%) were common pathogens. Peripheral limb emboli predicted reinfection (HR 4.118, 95% CI 1.471-11.528, p=0.007). Survival rates at 1, 2, and 5 years were 70.2%, 65.7%, and 57.3%, respectively. Age (HR 1.030, 95% CI 1.011 – 1.049, p=0.002), peripheral limb emboli (HR 2.994, 95% CI 1.509-5.940, p=0.002), and septic shock (HR 2.357, 95% CI 1.097-5.065, p=0.028) predicted mortality.

Conclusion: Infective endocarditis mortality rates remain high regardless of reinfection. Peripheral limb emboli independently determine reinfection and mortality. Careful management of this group may reduce morbidity and mortality.

Keywords: Infective endocarditis, Reinfection, Long-term mortality

1. INTRODUCTION

Infective endocarditis (IE) is a destructive condition typically triggered by bacterial infections, indicating an infection of the endocardial lining of the heart or foreign materials within the heart [1]. Despite its relative rarity, the estimated annual incidence of the disease ranges from 1.5 to 11.6 cases per 100,000 individuals [2]. While a decrease in IE incidence is expected with advancements in medical diagnosis and treatment, factors such as an aging population, increased use of intracardiac devices, prosthetic valves, intravenous (IV) injections, hemodialysis, and an increase in immunosuppressed patients contribute to its rise [3].

Despite advanced diagnostic and treatment methods, in-hospital mortality remains at 25%, with 1-year mortality rates at approximately 30% and 5-year mortality rates hovering around 45%, indicating a prognosis worse than many cancer types [4,5]. Prolonged IV antimicrobial treatment, the need for frequent valve surgeries, an extended hospital stay due to serious complications (e.g., cerebrovascular), and admission to the intensive care unit impose a significant financial burden on society [6]. Additionally, among IE patients who survive the initial episode, a noteworthy complication, recurrent IE, can occur in 2% to 31% of cases [7].

The 1-year mortality of patients experiencing recurrent IE is higher than that of those with a single IE episode, further increasing the financial burden due to repeated hospitalizations and additional treatment needs [8]. These striking figures underscore the significance of long-term outcomes in IE. In this context, our study aims to determine the long-term mortality risk among patients diagnosed with IE using modified Duke criteria [9], presenting at a tertiary referral center in Turkiye.

We intend to achieve this by examining the demographic characteristics, disease features, treatment strategies, and complications of these patients, ultimately contributing to more effective patient management in clinical practice. Additionally,

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we will present the findings of the investigation exploring factors influencing early and late reinfection, as well as long-term mortality in patients, and their impact on clinical outcomes.

2. PATIENTS and METHODS

Study Population

Between 2009 and 2019, a total of 204 consecutive adult patients with a definitive diagnosis of IE were retrospectively included in our tertiary care hospital. Inclusion criteria were defined as follows: 1) adult patients aged 18 years and older, and 2) patients with a definite diagnosis of IE according to modified Duke criteria. Eleven patients with incomplete data were excluded from the study, and an additional 15 patients could not be reached during follow-up, leaving 178 patients for evaluation. The diagnosis of IE in all suspected cases was confirmed by a multidisciplinary endocarditis team consisting of cardiologists, infectious disease specialists, and cardiovascular surgeons. The study protocol was approved by the Ethics and Research Committee of our hospital on 13.03.2024 with the Ethics Committee Decision numbered 2024.01-12 and complies with the principles in the Declaration of Helsinki.

Data Collection and Follow-up

All data relied on a systematic retrospective review of electronic medical records encompassing all patient documents, echocardiography, and laboratory results. Given that all patient records were linked to the national death reporting system, deaths occurring outside the hospital were also included. All patients were treated in accordance with predefined surgical indications and treatment algorithms outlined by the American Heart Association and the European Society of Cardiology [10,11]. Microbiological diagnosis was established through blood cultures (three sets of blood cultures taken half an hour apart), extracted material, or valve cultures. Before concluding negative blood culture endocarditis (BCNE), specific analyses including serological tests for more specific pathogens such as Bartonella, Mycoplasma, Brucella spp., and Chlamydia spp., etc., were conducted using enriched culture media. Transthoracic (TTE) and transesophageal (TEE) echocardiography were performed according to European guidelines for patients with clinical or microbiological suspicion of IE and for diagnosing intracardiac complications [12]. Evaluation using PET/CT was conducted when paravalvular extension, systemic, and cerebrovascular embolism could not be determined by CT and Duke criteria. The primary outcome of the study was all-cause mortality, while the secondary outcome was the occurrence of any early or late reinfection.

Definitions

Early reinfection was defined as recurrence of IE with the same pathogen (equals relapse) or a new episode caused by a different microorganism within 6 months after the index event. Late reinfection was defined as recurrence of IE with the same pathogen or a new episode caused by a different microorganism occurring 6 months after the index event [13]. Stroke was characterized by clinical and radiographic abnormalities consistent with acute stroke, encompassing both clinical presentations during treatment and stroke related to surgery. Peripheral embolization, excluding stroke, was defined as clinical and nuclear/radiographic abnormalities consistent with embolization. Diabetes Mellitus (DM) was defined as having at least two fasting plasma glucose levels ≥ 126 mg/dL or plasma glucose levels ≥ 200 mg/dL after meals or the use of antidiabetic drugs. Hypertension was defined as systolic blood pressure >;140 mmHg and/or diastolic blood pressure >;90 mmHg or current use of antihypertensive drugs by the patient. Heart failure was defined as a presentation including at least two of the following: NYHA class III-IV, acute decompensation on chest X-ray or echocardiogram, new peripheral edema.

Statistical Analysis

The normality of variables was evaluated utilizing Kolmogorov-Smirnov tests, histograms, and probability plots. Numeric variables are reported as mean ± standard deviation or median (interquartile range) depending on their distribution. Categorical variables are expressed as percentages (%). Numerical variables between two groups were compared using either Student's t-test or Mann-Whitney U test, while categorical variables were compared using Chi-square or Fisher's exact test. Kaplan-Meier modeling was utilized to depict the duration until the cessation of service events, serving as a proxy for mortality following aneurysm surgery. This analysis was conducted using SPSS 26.0 software (SPSS,Chicago, IL). Statistical comparisons of the time-to-event data for various interventions and controls were performed using log-rank tests and reported as median survival rates (years ± 95% CI). Additionally, all patients, a single-variable Cox proportional hazards model was utilized to compute hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) for long-term mortality. Multivariable Cox proportional models were employed to assess potential independent predictors for survival. The significance level was set at $p < 0.050$.

3. RESULT

A total of 178 patients with a mean age of 54.9 ± 15.4 years were included in the study, of which 63 (35.4%) were female. The patients were followed for an average of 40.3 ± 26.4 months. The baseline characteristics of the patients are detailed in Table 1. Reinfection occurred in a total of 21 (11.8%) patients, with 9 (5.1%) classified as early reinfection and 12 (6.7%) as late reinfection. While the characteristic features and comorbidities of the study group were similar in terms of reinfection, hemodialysis (p=0.003), and peripheral emboli (p = 0.006) were found to be higher in the group experiencing early and late reinfections. The most common infectious agents consisted of streptococci in 26.3% (47/178), Staphylococcus in 22.3% (40/178), and Enterococcus in 15.6% (28/178) of cases. Left-sided valve involvement was present in the majority of patients (90.5%). Isolated pacemaker lead endocarditis was observed in 21 (11.8%) patients, pulmonary valve endocarditis in 1 (0.6%) patient, and tricuspid valve endocarditis in 7 (3.9%) patients. Endocarditis related to substance abuse was identified in 5 (2.8%) patients. Congenital heart disease was present in 8 (4.5%) patients, with 1 being cyanotic and 7 non-cyanotic. Medical treatment along with surgery was administered to 69.8% of the patients.

Table I. *Characteristics and Comorbidities of the Study Group in terms of Reinfection*

	All patients	No reinfection	Early reinfection	Late reinfection	P Value
n (%)	**178 (100%)**	**157 (88.2%)**	**9 (5.1%)**	**12 (6.7%)**	
Age	54.9 ± 15.4	54.5 ± 15.5	58.7 ± 10.4	54.6 ± 16.1	0.750
Female (n, %)	63 (35.4%)	54 (34.4%)	4 (44.4%)	5 (41.7%)	0.742
DM (n, %)	29 (16.3%)	28 (17.8)	1 (11.1%)	0 (0%)	0.248
Hemodialysis (n, %)	9 (5.1%)	5 (3.2%)	1 (11.1%)	3 (25%)	0.003
LVEF (%)	53.7 ± 10.5	54.3 ± 10.7	46.1 ± 6	51.7 ±8.9	0.320
Immunosuppressive Treatment (n, %)	2 (1.1%)	2 (1.3%)	0 (0%)	0 (0%)	0.873
Stroke (n, %)					0.495
Ischemic stroke	13 (7.3%)	12 (7.6%)	1 (11.1%)	0 (0%)	
Hemorrhagic stroke	6 (3.4%)	5 (3.2%)	1 (11.1%)	0 (0)	
Septic Pulmonary Emboli (n, %)	18 (10.7%)	16 (10.9%)	2 (22%)	0 (0%)	0.260
Splenic and/or Renal Emboli (n, %)	12 (6,7%)	11 (7%)	0 (0%)	1 (8.3%)	0.699
Peripheral Limb Emboli (n, %)	14 (7.9%)	9 (5.7%)	3 (33.3%)	2 (16.7%)	0.006
Abscess (n, %)	21 (12.5%)	20 (13.6)	1 (11.1%)	0 (0%)	0.388
Treatment					0.596
Medical (n, %)	54 (30.2)	47 (29.7%)	2 (22.2%)	7 (77.8%)	
Surgical (n, %)	125 (69.8%)	111 (70.3)	5 (41.7%)	7 (58.3%)	
Substance Abuse (n, %)	5 (2.8%)	4 (2.5%)	0 (0%)	1 (8.3%)	0.440
Congenital Heart Disease (n, %)	8 (4.5%)	7 (4.4%)	1 (11.1%)	0 (0%)	0.474
Prosthetic valve endocarditis (n, %)	61(34.3 %)	54(34.4 %)	4(44.4 %)	3(25 %)	0.646
Causative Agents(n, %)					0.136
Streptococci	47 (26.3%)	43 (27.4%)	2 (22.2%)	2 (16.7%)	
MSSA	28 (15.6%)	22 (14%)	1 (11.1%)	5 (41.7%)	
MRSA	12 (6.7%)	10 (6.4%)	2(22.2%)	0 (0%)	
Enteroccoci	28 (15.6%)	25 (15.9%)	1 (11.1%)	2 (16.7%)	
BCNE	17 (9.5%)	17 (10.8%)	0 (0%)	0 (0%)	
CoNS	35 (19.6%)	31 (19.8%)	1 (11.1%)	3 (25%)	
Other	8 (4.5%)	7 (4.5%)	1 (11.1%)	0 (0%)	
Candida-Aspergillus	3 (1.7%)	2 (1.3%)	1 (11.1%)	0 (0%)	
Valve Involved (n,%) Mitral					0.508
	72 (40.4%)	64 (40.8%)	4 (44.4%)	4 (33.3%)	
Aortic	54 (30.3%)	49 (31.2%)	2 (22.2%)	3 (25%)	
Mitral + aortic	17 (9.6%)	16 (10.2%)	0 (0%)	1 (8.3%)	
Trikuspid	7 (3.9%)	5 (3.2%)	0 (0%)	2 (16.7%)	
Pacemaker	21 (11.8%)	16 (10.2%)	3 (33%)	2 (16.7%)	
Pulmonary	1 (0.6%)	1 (0.6%)	0 (0%)	0 (0%)	

BCNE: Blood culture-negative endocarditis, CoNS: Coagulase-negative Staphylococci, DM: diabetes mellitus, MSSA: methicillin-sensitive Staphylococcus aureu, MRSA: Methicillin-resistant Staphylococcus aureus, LVEF: Left ventricle ejection fraction

Table II. *Univariate and multivariate Cox regression analysis for endpoints. First reinfection (early and late reinfections combined)*

	Univariate analysis		Multivariate analysis	
	Hazard ratio 95%CI (lower-upper)	P value	Hazard ratio 95%CI (lower-upper)	P value
Age	1.007 (0.979-1.036)	0.620		
Gender	1.402 (0.591-3.327)	0.444		
DM	2.643 (1.095-6.379)	0.031	1.881 (0.750-4.715)	0.178
Hemodialysis	2.060 (0.946-4.487)	0.069		
LVEF	0.967 (0.936-0.999)	0.040	0.969 (0.936-1.003)	0.076
Peripheral Limb Emboli	14.949 (4.595-48.635)	<0.001	4.118 (1.471-11.528)	0.007
Surgical treatment	0.788 (0.316-1.970)	0.611		
Staphylococcal infection	1.224 (0.516-2.906)	0.646		

DM: diabetes mellitus, LVEF: Left ventricle ejection fraction

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Table III. *Univariate and multivariate Cox regression analysis for All-cause mortality.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio 95%CI (lower-upper)	P value	Hazard ratio 95%CI (lower-upper)	P value
Age	1.036 (1.019-1.054)	**<0.001**	1.030 (1.011-1.049)	**0.002**
Gender	1.308 (0.824-2.077)	0.254		
DM	1.282 (0.717-2.293)	0.401		
HT	1.537 (0.965-2.448)	0.070		
Stroke	0.843 (0.366-1.941)	0.688		
Hemodialysis	2.345 (1.076-5.109)	**0.032**	1.086 (0.443-2.658)	0.857
LVEF	0.967 (0.936-0.999)	**0.040**	0.993 (0.973-1.013)	0.504
Peripheral limb emboli	2.711 (1.422-5.169)	**0.002**	2.994 (1.509-5.940)	**0.002**
Re-endocarditis	1.706 (0.938-3.105)	0.080		
Septic shock	3.268 (1.663-6.422)	**0.001**	2.357(1.097-5.065)	**0.028**
Surgical treatment	0.461 (0.292-0.727)	**0.001**	0.644 (0.391-1.062)	0.085
Staphylococcal infection	1.521 (0.962-2.406)	0.073		

DM: diabetes mellitus,HT: Hypertension, LVEF: Left ventricle ejection fraction

When comparing patients with prosthetic valve endocarditis (PVE) and native valve endocarditis (NVE) in the index case, there was no significant difference in terms of reinfection incidence (p=0.530). There was no significant difference in the risk of early and late reinfection based on the microorganisms causing the index case. Any first re-infection, early, and late reinfection patients were combined for analysis. Univariate Cox regression analyses were conducted with all parameters to identify determinants of the first reinfection. Parameters such as DM (p=0.031), LVEF (p=0.040), and Peripheral emboli (p<0.001) were presented in Table II, showing a significant association with the first reinfection. In the multivariate Cox regression analysis with these parameters, Peripheral emboli (p=0.007) were identified as independent determinants for reinfection.

The in-hospital mortality rate was 18%, and the mortality rates at 1 year, 2 years, and 5 years were determined as 29.8%, 34.3%, and 42.7%, respectively. Among the 178 patients, 124 (69.7%) underwent surgical treatment, while 54 (30.3%) received only medical treatment. Univariate Cox regression analyses were conducted with all parameters to identify determinants of long-term mortality. Parameters such as Age (p<0.001), hemodialysis (p=0.032), LVEF (p=0.040), peripheral emboli (p=0.002), septic shock (p=0.001), and non-surgical treatment (p=0.001) were presented in Table III, showing a significant association with long-term mortality. In the multivariate Cox regression analysis with these parameters, Age (p=0.002), peripheral emboli (p=0.002), and septic shock (p=0.028) emerged as independent determinants of long-term mortality.

The Kaplan-Meier survival analysis indicated a significant increase in long-term mortality in patients with early reinfection and those treated solely with medical therapy (Log-rank: p=0.016, p<0.001). However, no significant difference was observed in terms of causative agents (Log-rank: p=0.082) (Figure 1).

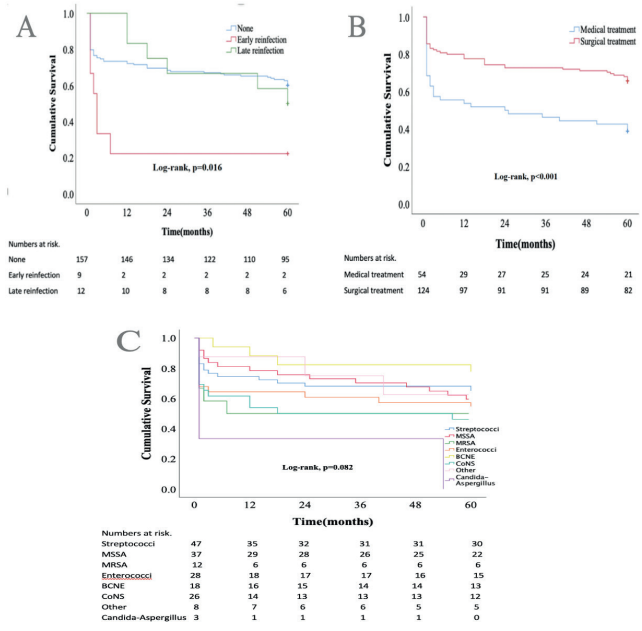

Figure 1. *Kaplan–Meier survival curves for Reinfection status in IE patient (A), medical and surgical treatment status (B), and causative agents (C).*

4. DISCUSSION

We report the outcomes of a retrospective cohort study evaluating the clinical characteristics and outcomes of adult patients diagnosed with IE treated at our tertiary cardiovascular center. The average follow-up duration for our study was 40.3 ± 26.4 months.

The main findings of our study are summarized below:

1. Reinfection occurred in a total of 21 patients (11.8%), with 9 cases (5.1%) classified as early reinfection and 12 cases (6.7%) as late reinfection.

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2. Peripheral emboli (p=0.007) were identified as independent determinants in the recurrence of infection.
3. In-hospital mortality was 18%, and mortality rates were determined to be 29.8% at 1 year, 34.3% at 2 years, and 42.7% at 5 years.
4. Age (p=0.002), peripheral emboli (p=0.002), and septic shock (p=0.028) emerged as independent predictors of long-term mortality.

The rates of early and late reinfection observed in our study were comparable to existing literature. We observed an incidence of 5.1% for early reinfection and 6.7% for late reinfection. The rate of early reinfection leading to prosthetic valve dysfunction was found to be 4%. Our findings align with recent studies suggesting an incidence range of 4% to 12% [14].

There is controversial data and conclusions in between studies in literature about re-infection of IE. In a study conducted by Heiro et al., IV drug use, DM and hemodialysis were identified as significant risk factors for recurrent episodes of IE [15]. In another study, theyconcluded that IV drug usage, prosthetic valve endocarditis and infection caused by S. Aureus were associated with re-infection [16]. Moreover, a study conducted by Thornhill et al., heart failure at presentation and the presence of a pacemaker were independent predictors [17]. In our study, only independent determinants of any reinfection were identified as peripheral emboli during the index case. In our cohort, statistically significant risk factors for reinfection did not include prosthetic valve, the type of pathogen causing IE, age, surgical treatment, and hemodialysis. Furthermore, in our study, DM and reduced LVEF during the index case were identified as risk factors for reinfection in univariate analysis, but they did not reach statistical significance in multivariate analysis.

Hemodialysis is a well-known factor associated with both recurrent infections and mortality. The presence of catheter-related bacteremia in recurrent IE and hemodialysis is not surprising. Studies have shown that healthcare-associated IE represents nearly one-third of all cases, and catheters are a significant source of infection in these patients [18]. In our study, hemodialysis was observed in 25% of late reinfections, but it was not identified as an independent variable in Cox regression analysis. This is likely due to the inadequacy of our sample size. Similarly, certain variables related to reinfection, such as intravenous drug dependence and Staphylococcus aureus, which have been observed in other studies [19,20], may not have been detected in our study due to the limited number of patients.

Despite all the advancements in diagnosis and treatment, IE continues to be a fatal disease in the long term. In our study, the mortality rates at 1, 2, and 5 years of follow-up were 29.8%, 34.3%, and 42.7%, respectively. Independent determinants of mortality were identified as age, peripheral limb emboli, and septic shock in multivariate Cox regression analysis.

Peripheral emboli have been found to be an independent predictor of both reinfection and IE mortality. In the study by Tahon et al., peripheral emboli were identified as an independent predictor of reinfection [13]. In the study by Jose Fabri et al., the frequency of symptomatic peripheral emboli was found to be 21.1% [21], and hospital mortality was significantly higher in patients with symptomatic peripheral emboli at the time of diagnosis. Additionally, in a recent study, consistent with our findings, age and peripheral embolic phenomena have been defined as an independent determinant of mortality [22].

Septic shock, independently of IE, is associated with high morbidity and mortality. In many studies conducted on patients with IE who meet the criteria for septic shock and have bacteremia, a significantly higher mortality has been observed [23,24]. In our study, both univariate and multivariate Cox regression analyses identified septic shock as an independent predictor of mortality (p=0.010).

Along with increasing age, patients tend to have more comorbidities, chronic illnesses, and increased susceptibility to infections. Similar to many other diseases, advanced age also contributes to mortality in IE. In our cohort, mortality significantly increased with age and was statistically significant. Our findings are in line with numerous studies in the literature [5,24,25].

In a study conducted using data from electronic databases in five different countries, it was observed that mortality associated with Staphylococcus infections in native valve IE was more pronounced [26]. Staphylococcal infections were linked to a higher mortality rate due to more frequent abscess formation, complete valve damage, and increased complication rates. In one study, the in-hospital mortality for Staphylococcus IE was reported as 45% [27]. Although our study showed a borderline significance in mortality when comparing Staphylococcal infections with other pathogens, no statistically significant difference was found (p=0.073).

The overall in-hospital mortality in our cohort was 18% (32/178). This rate was similar to the mortality reported in a study by Castillo and colleagues (21%) [28]. Patient characteristics, complications during the index case, and treatments administered lead to varying in-hospital mortality rates in different studies. In a study by Cebelli et al. [29], in-hospital mortality ranged from 15% to 25%, with a one-year mortality rate of 40%. In a study by Botelho and colleagues, a one-year mortality rate of 8.2% was reported [30]. Both of these studies are similar findings when compared to ours in terms of mortality rates.

Many contemporary studies have identified valve surgery in IE as a favorable prognostic factor [31]. In our study, although valve surgery was identified as an independent determinant of mortality and a good prognostic indicator in univariate Cox regression analysis, it did not reach statistical significance in multivariate analysis. We believe this difference may be attributed to our center being predominantly a referral center for patients requiring high-risk surgery. These variations likely stem from the complex pathology and clinical features of patients treated at our referral center, which accepts patients from various regions.

5. Conclusion

This study was conducted to understand the re-infection and mortality profiles of patients with IE treated at our tertiary

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cardiovascular center. Our findings indicate that early and late re-infection rates are consistent with similar studies in the literature, and peripheral emboli with septic shock are significant factors determining long – term mortality. This study may contribute to the development of strategies in IE treatment and optimization of in-hospital interventions.

Limitations

The primary limitation of our study is its retrospective cohort design and being single-centered. Acceptance of patients from all regions of the country at our center may result in higher mortality rates due to complex, complicated, and high-risk cases. Additionally, since out-of-hospital mortality causes could not be determined, mortality rates are provided as all-cause mortality rates.

Compliance with Ethical Standards

Ethics committee approval: The study was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee on 13.03.2024 with the approval number 2024.01-12. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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