The Clinical Course of Infective Endocarditis and Independent Predictors of In-Hospital Mortality

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ABSTRACT

Introduction: Despite advances in prevention, medical, and surgical treatment, the global prevalence of infective endocarditis (IE) has been gradually rising over the last two decades. However, the profile of IE varies by continent, geographic region, and hospital type. In this study, we aimed to investigate the epidemiological and clinical features of IE and to determine the factors predicting in-hospital mortality.

Patients and Methods: This retrospective study was carried out at a single tertiary health care hospital in Türkiye. A total of 104 consecutive patients (>18 years old) who were hospitalized with IE between January 2016 and August 2021 were included. Modified Duke criteria were used to diagnose IE. Demographic information (age and gender), underlying heart diseases, comorbidities, causative microorganisms, blood culture results, echocardiographic findings, cardiac and extracardiac complications, surgical requirements, and in-hospital mortality were all examined.

Results: The study included 104 IE cases (mean age: 57.2 ± 15.9 years; 59.6% males). Fifty-six patients (53.9%) had native valve IE, 37 patients (35.6%) had prosthetic valve IE, and four patients (3.8%) had device-related IE. Blood cultures were negative in 62 cases (59.6%). *Staphylococcus aureus* was the most common responsible microorganism in 17 patients [methicillin-sensitive *Staphylococcus aureus* in 13 (12.5%), methicillin-resistant *Staphylococcus* in four (3.8%)]. The overall in-hospital mortality rate was 30.8%. White blood cell count (OR= 1.002, 95% CI= 1.001-1.003) creatinine (OR= 1.45, 95% CI= 1.08-2.00), acute renal failure (OR= 8.60, 95% CI= 2.27-37.81), and cerebrovascular accidents (OR= 4.58, 95% CI= 1.21-18.85) were independent predictors of in-hospital mortality.

Conclusion: In line with developed countries, the epidemiology and causative pathogens of IE in Türkiye have been changing. Investigating these epidemiological and clinical changes may serve as a basis for strategies to be developed for the prevention and treatment of IE.

Key Words: Infective endocarditis; microbiology; epidemiology; mortality

Enfektif Endokarditin Klinik Seyri ve Hastane İçi Mortalitenin Bağımsız Öngörücüleri

ÖZET

Giriş: Önleme, tıbbi ve cerrahi tedavideki gelişmelere rağmen, enfektif endokarditin (EE) küresel prevalansı son yirmi yılda istikrarlı bir şekilde artmaktadır. Ancak, EE profili kıtaya, coğrafi bölgeye ve hastane türüne göre değişiklik göstermektedir. Bu çalışmada, EE'nin epidemiyolojik ve klinik özelliklerini araştırmayı ve hastane içi mortaliteyle ilişkili faktörleri belirlemeyi amaçladık.

Hastalar ve Yöntem: Bu retrospektif çalışma Türkiye'de üçüncü basamak bir hastanede gerçekleştirildi. Ocak 2016 ile Ağustos 2021 arasında EE tanısıyla hastaneye yatırılan toplam 104 ardışık hasta (>18 yaş) çalışmaya alındı. EE tanısında modifiye Duke kriterleri kullanıldı. Hastaların aşağıdaki verileri analiz edildi: Demografik bilgiler (yaş ve cinsiyet), altta yatan kalp hastalıkları, eşlik eden hastalıklar, neden olan mikroorganizmalar, kan kültürü sonuçları, ekokardiyografik bulgular, kardiyak ve ekstrakardiyak komplikasyonlar, cerrahi gereksinimler ve hastane içi mortalite.

Bulgular: Toplam 104 EE olgusu (ortalama yaş: 57.2 ± 15.9 yıl; %59.6 erkek) çalışmaya dahil edildi. Elli altı hastada (%53.9) nativ kapak endokarditi, 37 hastada (%35.6) protez kapak endokarditi ve dört hastada (%3.8) cihaza bağlı enfektif endokardit tespit edildi. Altmış iki olguda (%59.6) kan kültürü negatifti. *Staphylococcus aureus* 17 hastada en sık sorumlu mikroorganizmaydı [13 hastada (%12.5) metisiline duyarlı *Staphylococcus aureus*, dört hastada (%3.8) metisiline dirençli *Staphylococcus aureus*]. Genel hastane içi ölüm oranı %30.8 bulundu. Beyaz kan hücresi sayısı (OR= 1.002, %95 CI= 1.001-1.003), kreatinin (OR= 1.45, %95 CI= 1.08-2.00), akut böbrek yetmezliği (OR= 8.60, %95 CI= 2.27-37.81) ve serebrovasküler olaylar (OR= 4.58, %95 CI= 1.21-18.85), hastane içi mortalite için bağımsız öngörücüler olarak bulundu.

Sonuç: Gelişmiş ülkelere paralel şekilde, Türkiye'de de EE'nin epidemiyolojisi ve etken patojenleri değişim göstermektedir. Bu epidemiyolojik ve klinik değişikliklerin araştırılması, EE'nin önlenmesi ve tedavisine yönelik geliştirilecek stratejiler için bir temel teşkil edebilir.

Anahtar Kelimeler: Enfektif endokardit; mikrobiyoloji; epidemiyoloji; ölüm oranı

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INTRODUCTION

Infective endocarditis (IE) is an infectious disease of the endocardial surface of the heart with pre-existing lesions or on intracardiac foreign materials[1]. Despite advances in prevention, and medical and surgical treatment, the global prevalence of infective endocarditis (IE) has been gradually rising over the last two decades[2-4]. However, the profile of IE varies by continent, geographic region, and hospital type. While the main cause in developed countries is the increasing incidence of degenerative valvular heart disease and comorbid diseases with increasing age, chronic rheumatic heart disease (CRHD) still remains the main issue in developing countries[5].

The diverse clinical course and ever-changing epidemiological profile of IE pose diagnostic and management challenges. The presentation and progression of IE are highly variable, depending on host factors (such as pre-existing diseases, prosthetic heart valves, or implanted cardiac devices, as well as immune response modulators), the pathogen involved, and the sufficiency of the given treatment (antibiotics, complication management, surgery). Because of such differences, a proper understanding of the epidemiology and clinical features of IE in health care settings, including the pathogens that cause IE, may provide an opportunity to improve the clinical management of the disease.

In this study, we aimed to investigate the epidemiological, clinical, laboratory, and microbiological features of IE and to determine the factors predicting in-hospital mortality.

PATIENTS and METHODS

Study Population

This retrospective study was carried out at a single tertiary hospital in Türkiye. A total of 104 consecutive patients (>18 years old) who were hospitalized with IE between January 2016 and August 2021 were enrolled. The clinical data of the patients were collected from the electronic medical records. Patients who did not meet the definitive diagnostic criteria and whose clinical follow-up records were missing were excluded. Demographic information (age and gender), underlying heart diseases, comorbidities, causative microorganisms, blood culture results, echocardiographic findings, cardiac and extracardiac complications, surgical requirements, and in-hospital mortality were all examined. The study was reviewed and approved by the institutional ethics committee (Decision number: 2022/1/567).

Echocardiographic and Laboratory Examinations

The results of the initial routine laboratory tests during hospitalization as well as blood cultures were reported. Blood was collected according to the microbiological recommendations for the diagnosis of IE and sent to the institutional microbiology laboratory[6]. Automated hemoculture systems were used to perform the blood cultures. Serological tests were also performed for epidemiologically relevant pathogens (i.e., *Brucella* spp.) when clinically suspected. All patients had undergone transthoracic and/or transoesophageal echocardiographic (TEE) investigations to determine the location and extent of vegetation, the type of valve involved, and any local cardiac complications. TEE was performed on all patients who had a high initial risk (prosthetic heart valves, congenital heart diseases, intracardiac devices, previous endocarditis, or heart failure).

Definitions

Modified Duke criteria were used to diagnose IE[6]. IE was categorized as native-valve IE (NVIE), prosthetic valve IE (PVIE), and cardiac device-related IE (DRIE)[6]. DRIE was defined as IE occurring on pacemaker or defibrillator wires with or without associated valve involvement. PVIE was further subclassified into two groups: Early-onset (≤12 months postoperatively) or late-onset (>12 months postoperatively)[7].

Statistical Analysis

The analysis was performed using R software (version 4.0.1). Descriptive statistics were used to summarize patients' demographic and clinical characteristics. Continuous variables with normal distribution are expressed as mean ± standard deviation (SD) and continuous variables without normal distribution are expressed as median and interquartile range (IQR). Absolute values and percentages are used to express categorical data. The normal distribution was tested using the Kolmogorov-Smirnov test. Logistic regression analysis was performed in order to identify independent determinants of in-hospital mortality. All variables associated with a value of <0.05 in the univariate regression were incorporated into a stepwise, multivariate regression analysis. Two-sided p-values <0.05 were considered statistically significant.

RESULTS

One hundred and four IE cases (mean age= 57.2 ± 15.9 years; 59.6% males) were included in the study. The demographic, clinical, and laboratory characteristics of the study population are summarized in Table 1. Hypertension was the most prevalent comorbid disease (32.7%). The most common predisposing condition for IE was prosthetic valve disease (35.5%), followed by degenerative valve disease (33.6%) and the presence of a cardiac device or venous catheter (10.5%). Mean hemoglobin levels of patients were 9.9 ± 1.8 g/dL and white blood cell (WBC) counts were 12.1 ± 6.8 x 10^3/mL. C-reactive protein (CRP) and albumin levels were 24 ± 41 mg/L and 3.1 ± 0.6 g/dL, respectively.

Table 1. Demographic, clinical, and laboratory characteristics of patients with infective endocarditis

Variables	n (%)	Mean ± SD	Range
Age, (years)		57.2 ± 15.9	22-87
Gender, (male)	62 (59.6)		
Medical history			
Hypertension	34 (32.7)		
Diabetes mellitus	15 (14.4)		
Coronary heart disease	26 (25.0)		
Heart failure	15 (14.4)		
Chronic kidney disease (GFR< 15)	17 (16.3)		
Predisposing conditions			
Previous IE	5 (4.8)		
Prosthetic heart valve	37 (35.5)		
Cardiac device or venous catheter	11 (10.5)		
IV drug user	1 (0.9)		
For native valve IE			
Degenerative valve disease	35 (33.6)		
Rheumatic valve disease	7 (6.7)		
Mitral valve prolapse	8 (7.7)		
Bicuspid aortic valve	4 (3.8)		
Congenital heart defects	2 (1.9)		
Laboratory characteristics			
Haemoglobin, g/dL		9.9 ± 1.8	6.7-16.4
White blood cell count, $x10^3$/mL		12.1 ± 6.8	2.1-35.5
Platelet count, $x10^3$/mL		237 ± 99	56-616
Neutrophil count, $x10^3$/mL		9.8 ± 6.2	1.2-31.2
Lymphocyte count, $x10^3$/mL		1.3 ± 6.8	0.4-12.2
Creatinine, mg/dL		1.73 ± 1.87	0.2-9.3
ALT, IU/L		39 ± 67	3-541
AST, IU/L		39 ± 44	10-311
C-reactive protein, mg/L		24 ± 41	0.3-221
Albumin, g/dL		3.1 ± 0.6	1.9-4.6

SD: Standart deviation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IE: Infective endocarditis, INR: International normalized ratio, GFR: Glomerular filtration rate.

Echocardiography findings and causative microorganisms of IE patients are shown in Table 2. TEE was performed in 72 (69.2%) cases. Vegetation was detected in 98 patients [<10 mm in 57 (54.8%), 10-20 mm in 26 (25.0%) and >20 mm in 15 (14.4%)]. Fifty-six patients (53.9%) had NVIE, 37 patients (35.6%) had PVIE, and four patients (3.8%) had DRIE. Aortic valve was the most frequently involved in NVIE (25.0%).

Blood cultures were negative in 62 cases (59.6%). *Staphylococcus aureus* was the most common causative microorganism in 17 patients methicillin-sensitive (MS) *Staphylococcus aureus* in 13 (12.5%), methicillin-resistant (MR) *Staphylococcus* in four (3.8%), followed by coagulase-negative *Staphylococci* in eight patients (MS coagulase-negative *Staphylococci* in seven (6.7%), MR coagulase-negative *Staphylococci* in one (0.9%), and *Enterococcus faecalis* in five patients (4.8%).

Table 2. Echocardiography findings and causative microorganisms of IE patients

Variables	n (%)	Variables	n (%)
Performance of TEE	72 (69.2)	Vegetation	98 (94.2)
Performance of CT	37 (35.3)		
Prosthetic valve IE		Vegatation size	
Mechanical mitral	9 (8.7)	<10 mm	57 (54.8)
Bioprosthetic mitral	3 (2.9)	10-20 mm	26 (25.0)
Mechanical aortic	9 (8.7)	>20 mm	15 (14.4)
Bioprosthetic aortic	2 (1.9)	Blood culture negative IE	62 (59.6)
Bioprosthetic triscuspid	1 (0.9)	*Staphylococcus aureus*	
Bioprosthetic pulmonary	3 (2.9)	MRSA	4 (3.8)
Multiple (prosthetic+prosthetic or prosthetic+native)	10 (9.6)	MSSA	13 (12.5)
Early prosthetic valve IE	16 (15.4)	CoNS	
Late prosthetic valve IE	21 (20.2)	Methicillin-resistant CoNS	1 (0.9)
		Methicillin-sensitive CoNS	7 (6.7)
Native valve IE			
Mitral	14 (13.5)	Viridans *Streptococcus*	2 (1.9)
Aortic	26 (25.0)	*Enterococcus faecalis*	5 (4.8)
Triscuspid	5 (4.8)	*Brucella melitensis*	1 (0.9)
Pulmonary	2 (1.9)	Gram-negative bacilli	4 (3.8)
Multiple (native+native)	9 (8.7)	*Candida albicans*	2 (1.9)
Non-valve		Other	5 (4.8)
Cardiac device	4 (3.8)		
Unidentified or other regions	7 (6.7)		

CONS: Coagulase-negative *Staphylococci*, CT: Computed tomography, IE: Infective endocarditis, MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-sensitive *Staphylococcus aureus*, TEE: Transoesophageal echocardiography.

The distribution of cardiac and systemic complications and treatment management of IE patients are shown in Table 3. Cerebrovascular accidents (20.2%) were the most common systemic complication, followed by acute renal failure (18.3%), congestive heart failure (8.7%), embolic events (7.7%), and splenic abscess (0.9%). Valvular perforation was the most prevalent complication of perivalvular extension (7.7%). In 54 patients (51.9%), surgery was performed. Surgical indications were as follows: 19 patients (35.1%) with acute heart failure/severe valvular regurgitation; 18 patients (33.3%) with embolic events; 10 patients (18.5%) with uncontrolled infection; and seven patients (12.9%) with vegetation >20 mm. Thirty-five patients underwent mechanical valve implantation, and nine patients underwent bioprosthetic valve implantation. Percutaneous lead extraction was performed on four patients. The total median length of hospitalization was 23$^{(12-34)}$ days. Thirty-two patients died during hospital stays. The overall in-hospital mortality rate was 30.8%. The mortality for medically treated patients was 42.0% and for surgically treated patients was 20.3% ($p< 0.05$).

Univariate and multivariate analysis for factors associated with in-hospital mortality are shown in Table 4. In univariate logistic regression analysis, age (OR= 1.04, 95% CI= 1.01-1.07), hemoglobin (OR= 0.61, 95% CI= 0.45-0.83), white blood cell count (OR= 1.001, 95% CI= 1.000-1.002), creatinine (OR= 1.25, 95% CI= 1.01-1.56), albumin (OR= 0.34, 95% CI= 0.15-0.79), prosthetic valve IE (OR= 3.58, 95% CI= 1.49-8.59), acute renal failure (OR= 10.42, 95% CI= 3.31-32.78), and cerebrovascular accidents (OR= 4.20, 95% CI= 1.54-11.41) were associated with mortality. In multivariate analysis, white blood cell count (OR= 1.002, 95% CI= 1.001-1.003) creatinine (OR= 1.45, 95% CI= 1.08-2.00), acute renal failure (OR= 8.60, 95% CI= 2.27-37.81), and cerebrovascular accidents (OR= 4.58, 95% CI= 1.21-18.85) were independent predictors of in-hospital mortality. High hemoglobin level (OR= 0.59, 95% CI= 0.37-0.89) was found to be associated with a favorable prognosis in infective endocarditis.

Table 3. Complications and management of IE patients

Variables		Variables	
Complications		Treatment	
Perivalvular extension		Medical	46 (44.2)
Perivalvular abscess	7 (6.7)	Surgery	54 (51.9)
Pseudoaneurysm	4 (3.8)	Mechanical valve implantation	35 (33.7)
Perforation	8 (7.7)		
Dehiscence	7 (6.7)	Bioprosthetic valve implantation	9 (8.7)
Intracardiac fistula	1 (0.9)		
Congestive heart failure	9 (8.7)	Annuloplasty	2 (1.9)
Acute renal failure	19 (18.3)	Other	8 (7.7)
Cerebrovascular accidents	21 (20.2)	Lead extraction	4 (3.8)
Embolic phenomenon	8 (7.7)	*Length of hospital stay, days	23.0 [12-34]
Splenic abscess	1 (0.9)	In-hospital mortality	32 (30.8)

Data are expressed as n (%) or *median (IQR).

Table 4. Univariate and multivariate analyses for independent predictors of in-hospital mortality

	Univariate			Multivariate		
Variables	**OD**	**95% CI**	**p**	**OD**	**95% CI**	**p**
Age	1.04	1.01-1.07	0.01	1.02	0.99-1.06	0.170
Gender (male)	0.68	0.29-1.58	0.36			
DM	0.52	0.13-1.98	0.33			
Coronary heart disease	1.00	0.38-2.61	0.99			
Hemoglobin	0.61	0.45-0.83	0.002	0.59	0.37-0.89	0.011
White blood cell count	1.001	1.000-1.002	0.007	1.002	1.001-1.003	0.012
Platelet count	1.001	0.999-1.002	0.11			
Creatinine	1.25	1.01-1.56	0.04	1.45	1.08-2.00	0.014
Albumin	0.34	0.15-0.79	0.01	0.85	0.25-2.57	0.780
C-reactive protein	1.008	0.998-1.018	0.102			
Prosthetic valve IE	3.58	1.49-8.59	0.004	3.31	0.98-12.21	0.053
*Perivalvular complications	0.76	0.25-2.34	0.64			
Acute renal failure	10.42	3.31-32.78	<0.001	8.60	2.27-37.81	0.001
Cerebrovascular accidents	4.20	1.54-11.41	0.001	4.58	1.21-18.85	0.024
Congestive heart failure	1.91	0.48-7.66	0.36			

*Perivalvular abscess, pseudoaneurysm, perforation, dehiscence or intracardiac fistula.
CI: Confidence interval, DM: Diabetes mellitus, OD: Odds ratio, IE: Infective endocarditis

DISCUSSION

The key findings of the current study are as follows:

1) Although the epidemiological characteristics and causative microbiological profile of IE are comparable to those of developed countries, certain differences still exist;

2) In-hospital mortality for IE was 30.8%, with more than half of the patients having a complicated clinical course;

3) Acute renal failure and cerebrovascular accidents were the strongest predictors of in-hospital mortality.

Our cohort's mean age was 58 years, which was older than in previous studies in Türkiye but still younger than in developed countries[8-10]. The fact that IE was diagnosed at a younger age in previous studies conducted in Türkiye could be related to the higher CRHD rate[11]. In the current study, CRHD was found to be the third most common predisposing valve lesion for NVE, after degenerative valve disease and mitral valve prolapse. Only one patient (1.1 percent) with tricuspid valve endocarditis had intravenous drug use as a risk factor. In comparison to high-income countries, where the rate of IV drug use among IE cases is around 10%[5], this rate was very low. Our findings are consistent with previous research, which indicates that there is a slow but noticeable shift from CRHD to degenerative heart diseases as a significant risk factor in the etiology of IE[5,12,13].

Culture-negative endocarditis accounted for 59.6% of cases in our study. Being a referral cardiology center explains the numerically high percentage. The high rate of culture-negative endocarditis was primarily due to the use of antimicrobials prior to admission to our center. Other possible causes might include non-culturable organisms and a lack of appropriate culturing techniques. Our study's retrospective nature limits our ability to precisely clarify the reasons. *Staphylococcus* species were the most commonly isolated organisms in blood culture. *Staphylococci* have increased proportionally in recent years due to an increase in healthcare-associated endocarditis[14]. Our findings confirm that staphylococcal organisms have surpassed streptococcal organisms as the main cause of IE, with a corresponding decrease in the frequency of viridans streptococcal infections over the last decade[15,16].

In IE, four major factors influence prognosis: Patient characteristics, the presence or absence of systemic and cardiac complications, the causative microorganism, and echocardiographic findings[6]. In the present study, acute renal failure and cerebrovascular accidents were identified as the most significant predictors of in-hospital mortality. Acute renal failure is primarily explained by immune complex deposition-induced glomerulonephritis. Other possible factors include acute interstitial nephritis and acute tubular necrosis due to nephrotoxic agents, as well as cortical necrosis caused by inadequate renal perfusion. Buchholtz et al. found that every 10 mL/min decrease in estimated endogenous creatinine clearance increased the risk of mortality by 23.1%[17]. Nevertheless, risk factors for acute renal injury at the onset of endocarditis are still being questioned. Embolic events (EE) are common in IE (20% to 50% of cases) and carry a high risk of morbidity and mortality[6,15]. Furthermore, the embolic event is clinically silent in 15% of IE patients[18]. In a multicenter study using admission-screening CT imaging in 384 patients presenting with IE, 26% of cases had one site of embolism, and 9% had multiple sites of embolism, with the central nervous system (38%) being the most commonly affected[19]. In a study of 130 patients with IE, cerebral magnetic resonance imaging detected acute ischemic lesions in 52%, and only 12% had acute neurologic symptoms[20]. The wide variation in the frequency of cerebrovascular events reported in the literature can be attributed to a preference for different imaging modalities as well as the use of different indications to employ the relevant imaging techniques. Prompt and effective treatment and prevention of these complications can be decisive in minimizing the negative consequences of IE.

In recent years, the number of patients with cardiac devices has increased dramatically, and this trend is expected to continue as the indications for their use expand and the population ages. The most important aspects of DREI management are antimicrobial therapy and complete device removal. Four patients in our study had lead extraction performed percutaneously. One patient died as a result of DREI. The size of our study population was insufficient to determine the mortality rate and prognosis in DREI patients.

In most series, including Turkish cohorts, surgery is performed in 23-69% of patients with IE[21-23], and our study was consistent with this prevalence (51.9%). Our cohort's mortality rate was 30.8%, which is slightly higher than the current literature (12-30%)[24-26]. Because our hospital is a referral center for surgical intervention, the higher mortality rate could be attributed to the referral of more complicated cases.

This study has some limitations that need to be addressed.

1) It was conducted at a single tertiary referral center and the study sample was relatively small. Prospective multicenter studies are needed to draw more robust conclusions regarding the nationwide etiology and mortality of IE in Türkiye.

2) Some information regarding the clinical course of IE might not be recorded, which may affect the precise determination of the clinical significance of some findings.

3) Due to the retrospective study design, we currently have no long-term follow-up data for IE patients. Therefore, we are unable to analyze these patients' long-term outcomes.

CONCLUSION

In conclusion, despite recent advances in both diagnosis and treatment, IE continues to be associated with high mortality rates. In line with developed countries, the epidemiology and causative pathogens of IE in Türkiye have been changing. Investigating these epidemiological and clinical changes may serve as a basis for strategies to be developed for the prevention and treatment of IE.

Ethics Committee Approval: The approval for this study was obtained from Kartal Koşuyolu High Specialization Training and Research Hospital Ethics Committee (Decision no: 2022/1/567, Date: 11.01.2022).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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