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The More Vulnerable, the More Fatal: Predictors for Mortality in Patients with Dreadful Infective Endocarditis

Ne Kadar Savunmasız, O Kadar Ölümcül: Korkutucu İnfektif Endokarditli Hastalarda Mortalitenin Belirleyicileri

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ABSTRACT

Introduction: *Infective endocarditis and its complications are highly associated with morbidity and mortality. In this study, we aimed to determine independent predictors for mortality in patients with infective endocarditis.*

Materials and Methods: *In this single-center retrospective study, all patients with definitive infective endocarditis, according to the modified Duke criteria, between January 2015 and December 2023 were included. Mortality was defined as in-hospital all-cause death. Univariate analysis and multivariate regression models were performed.*

Results: *A total of 69 patients were included. Of those, 55.1% were male, and the median age was 61 (50-71) years. The rate of in-hospital mortality was 46.4% (n= 32). The most common comorbidity was chronic kidney disease (n= 34, 49.3%). Twenty-three patients (33.3%) were receiving chronic dialysis. Staphylococcus aureus bacteremia was observed in 36 (52.2%) patients. The rate of methicillin resistance among S. aureus was 38.9% (n= 14). Fifty-six patients (81.2%) had at least one complication. In univariate analysis, age (p= 0.002), presence of at least one comorbidity (p= 0.036), chronic kidney disease (p= 0.043), prosthetic valve endocarditis (p= 0.036), bacteremia with methicillin-resistant S. aureus (p= 0.043), and presence of complication (p= 0.023) were associated with in-hospital mortality. In multivariate regression models, advanced age (OR= 1.06, CI= 1.01-1.11, p= 0.027), prosthetic valve endocarditis (OR= 12.17, CI= 1.18-125.67, p= 0.036), and presence of complication (OR= 6.18, CI= 1.08-35.24, p= 0.040) were independent predictors for in-hospital mortality.*

Conclusion: *Infective endocarditis is a complex and dreadful disease, with nearly half of the patients succumbing to it. Although chronic kidney disease was the most common comorbidity among patients with infective endocarditis, neither chronic kidney disease nor chronic dialysis was independently associated with in-hospital mortality. Older adults with complicated prosthetic valve endocarditis should be prioritized as high-risk targets in the management of infective endocarditis.*

Key Words: *Infective endocarditis; Bacteremia; Dialysis; Mortality; Staphylococcus aureus*

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ÖZ

Ne Kadar Savunmasız, O Kadar Ölümcül: Korkutucu İnfektif Endokarditli Hastalarda Mortalitenin Belirleyicileri

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Giriş: *İnfektif endokardit ve komplikasyonları morbidite ve mortalitede artışla ilgilidir. Bu çalışmada, infektif endokarditli hastalarda mortalitenin bağımsız belirleyicilerinin belirlenmesi amaçlanmıştır.*

Materyal ve Metod: *Bu tek merkezli retrospektif çalışmaya, Ocak 2015 ile Aralık 2023 tarihleri arasında modifiye Duke kriterlerine göre kesin infektif endokardit tanısı alan tüm hastalar dahil edildi. Mortalite, hastanede tüm nedenlere bağlı ölüm olarak tanımlandı. Tek değişkenli analiz ve çok değişkenli regresyon modelleri uygulandı.*

Bulgular: *Toplam 69 hasta dahil edildi. Bunların %55.1'i erkekti ve ortanca yaş 61 (50-71) yıldı. Hastane içi mortalite oranı %46.4 (n= 32) idi. En sık eşlik eden hastalık kronik böbrek hastalığıydı (n= 34, %49.3). Hastaların 23 (%33.3)'ü kronik diyaliz alıyordu. Hastaların 36 (%52.2)'sında Staphylococcus aureus bakteremisi görüldü. S. aureus'ta metisiline direnç oranı %38.9 (n= 14) idi. Elli altı hastada (%81.2) en az bir komplikasyon görüldü. Tek değişkenli analizde yaş (p= 0.002), en az bir komorbidite varlığı (p= 0.036), kronik böbrek hastalığı (p= 0.043), protez kapak endokarditi (p= 0.036), metisiline dirençli S. aureus bakteremisi (p= 0.043) ve komplikasyon varlığı (p= 0.023) hastane içi mortalite ile ilişkiliydi. Çok değişkenli regresyon modellerinde ileri yaş (OR= 1.06, CI= 1.01-1.11, p= 0.027), protez kapak endokarditi (OR= 12.17, CI= 1.18-125.67, p= 0.036) ve komplikasyon varlığı (OR= 6.18, CI= 1.08-35.24, p= 0.040) hastane içi mortalitenin bağımsız belirleyicileriydi.*

Sonuç: *İnfektif endokardit karmaşık ve korkunç bir hastalıktır ve hastaların neredeyse yarısı ölmüştür. Kronik böbrek hastalığı, infektif endokarditli hastalar arasında en sık görülen komorbidite olmasına rağmen ne kronik böbrek hastalığı ne de kronik diyaliz, bağımsız olarak hastane içi mortaliteyle ilişkilendirilmiştir. Komplike protez kapak endokarditi olan ileri yaştaki yetişkinler, infektif endokarditin tedavisinde yüksek riskli öncelikli hedef olarak değerlendirilmelidir.*

Anahtar Kelimeler: *İnfektif endokardit; Bakteremi; Diyaliz; Mortalite; Staphylococcus aureus*

INTRODUCTION

Infective endocarditis and its complications are highly associated with morbidity and mortality[1-3]. It is known that timely diagnosis and early antimicrobial stewardship are vital for reducing mortality. In addition, sometimes surgical intervention is necessary for complicated cases in the management of infective endocarditis. Infective endocarditis is associated with various complications. Delays in treatment increase the risk of complications, including sepsis, septic embolism, valvular regurgitation, and heart failure, and may result in mortality[4].

Poor prognosis may be associated with age, causative agent, comorbidities, complications, vegetation size, and valvular involvement[1,5,6]. However, mortality rates and risk factors for death in infective endocarditis may vary based on local and epidemiological differences. Therefore, there is a need to explore hospital-based mortality rates and risk factors in these patients. In this study, we aimed to determine independent predictors for mortality in patients with infective endocarditis.

MATERIALS and METHODS

In this single-center retrospective study, all hospitalized patients (≥18 years old) with definitive infective endocarditis, according to the modified Duke criteria, at Haseki Training and Research Hospital between January 2015 and December 2023 were included. Patients who were transferred to another hospital and had missing data on in-hospital mortality were excluded from the study.

Patients' age, demographic characteristics, underlying comorbidities, symptoms and findings, laboratory parameters [leukocyte count, hemoglobin, platelet count, C-reactive protein

(CRP), procalcitonin, erythrocyte sedimentation rate], echocardiography findings (valve involvement, vegetation size, heart failure findings), the need for surgery, the complications, microbiological agents, and clinical outcomes were recorded.

Additional serological tests for culture-negative endocarditis were ordered based on local epidemiological data, including Rose-Bengal, Wright, and Coombs Wright tests, *Coxiella burnetii* phase 1 IgG, histopathological examination, tuberculosis culture, and polymerase chain reaction. Three of the twenty patients refused treatment, seven required surgery, and the remaining ten patients were referred due to a lack of availability in our intensive care unit. These patients were excluded from our study as their mortality data could not be accessed.

Our primary outcome was mortality, defined as in-hospital all-cause death. All procedures were performed in accordance with the ethical standards outlined in the Declaration of Helsinki. This study was approved by the Ethics Committee of Haseki Training and Research Hospital Scientific Research (approval number: 49-2024 date: 27.06.2024). Written informed consent was waived, given the retrospective nature of this study.

Statistical Analysis

Continuous variables were described as medians with 25^{th} and 75^{th} percentiles, while categorical variables were presented as numbers and percentages. Chi-square and Fisher's exact tests were performed to compare categorical variables. While the Independent sample T-test was performed for variables with normal distribution, the Mann-Whitney U test was performed for variables without normal distribution. Univariate analyses and multivariate regression models were performed. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Independent predictors were identified using multivariate logistic regression analysis. Statistical Package for Social Sciences (SPSS) 20.0 version was used for statistical analyses. A p-value of <0.05 was considered statistically significant.

RESULTS

After excluding 20 patients with missing data on in-hospital mortality, a total of 69 patients were included in the study. Of those, 55.1% were male, and the median age was 61 (50-71) years. The rate of in-hospital mortality was 46.4% (n= 32). Fifty-two patients (75.4%) had at least one comorbidity. The most common comorbidity was chronic kidney disease (n= 34, 49.3%), followed by hypertension (n= 32, 46.4%), diabetes mellitus (n= 28, 40.6%), and chronic artery disease (n= 23, 33.3%). Twenty-three patients (33.3%) were receiving chronic dialysis. Fifty-six patients (81.2%) had at least one complication. Demographic characteristics of survived and deceased patients with infective endocarditis are presented in Table 1.

The median age was higher in patients who died compared to those who survived (66.5 vs. 52 years, p< 0.001). The presence of comorbidity (at least one) (87.5% vs. 64.9%, p= 0.03) and having a prosthetic valve (2.7% vs. 21.9%, p= 0.021) were more frequent in deceased patients than in survivors. Deceased patients were more likely to have at least one or more complications compared to survivors (93.8% vs. 70.3%, p= 0.013) (Table 1).

The median urea level was significantly higher in patients who died than in those who survived (97 vs. 52 mg/dL, p= 0.001). Leukocyte count, hemoglobin, platelet count, CRP, procalcitonin, and erythrocyte sedimentation rate did not differ between survived and deceased patients. Table 2 compares the laboratory parameters with the median and IQR values.

Staphylococcus aureus bacteremia was observed in 36 (52.2%) patients. The rate of methicillin resistance among *S. aureus* was 38.9% (n= 14). The distribution of microbiological agents is shown in Table 3. Methicillin-resistant *S. aureus* (MRSA) was more prevalent in deceased patients than survivors (31.3% vs. 10.8%, p= 0.035).

In univariate analysis, age (p= 0.002), presence of at least one comorbidity (p= 0.036), chronic kidney disease (p= 0.043), prosthetic valve endocarditis (p= 0.036), bacteremia with MRSA (p= 0.043), and presence of complications (p= 0.023) were associated with in-hospital mortality (Table 4). Multivariate regression models revealed that advanced age (OR= 1.06, CI= 1.01-1.11, p= 0.027), prosthetic valve endocarditis

Table 1. Comparison of demographic and clinical characteristics of patients with infective endocarditis

Parameters		Total, n (%)	Survived, n (%)	Deceased, n (%)	p
Age (years), median (25th and 75th percentiles)		61 (50-71)	52 (42-64)	66.5 (59-78.5)	**<0.001**
Gender	Female	31 (44.93)	18 (48.65)	13 (40.63)	0.54
	Male	38 (55.07)	19 (51.35)	19 (59.38)	
Hemodialysis		23 (33.3)	13 (35.14)	10 (31.25)	0.73
Non-dialysis predisposing condition		35 (50.72)	17 (45.95)	18 (56.25)	0.39
Acute rheumatic fever		5 (7.25)	4 (10.81)	1 (3.13)	0.36
Prosthetic valve		8 (11.59)	1 (2.7)	7 (21.88)	**0.02**
Intracardiac device		1 (1.45)	1 (2.7)	0 (0)	1
Bicuspid aorta		1 (1.45)	1 (2.7)	0 (0)	1
Degenerative valve		15 (21.74)	9 (24.32)	6 (18.75)	0.77
Comorbidity (at least one)		52 (75.36)	24 (64.86)	28 (87.5)	**0.03**
Chronic artery disease		23 (33.33)	11 (29.73)	12 (37.5)	0.49
Diabetes mellitus		28 (40.58)	13 (35.14)	15 (46.88)	0.32
Hypertension		32 (46.38)	14 (37.84)	18 (56.25)	0.12
Chronic heart failure		9 (13.04)	3 (8.11)	6 (18.75)	0.28
Chronic kidney disease		34 (49.28)	14 (37.84)	20 (62.5)	**0.04**
Immunosuppression		4 (5.8)	1 (2.7)	3 (9.38)	0.33
Cirrhosis		1 (1.45)	0 (0)	1 (3.13)	0.46
Autoimmune disease		2 (2.9)	1 (2.7)	1 (3.13)	1
Malignancy		6 (8.7)	2 (5.41)	4 (12.5)	0.4
Valve involvement		52 (75.36)	30 (81.08)	22 (68.75)	0.23
	Mitral	31 (44.93)	16 (43.24)	15 (46.88)	
	Aorta	11 (15.94)	7 (18.92)	4 (12.5)	
	Aortic and mitral	1 (1.45)	0 (0)	1 (3.13)	
	Tricuspid	7 (9.15)	5 (13.51)	2 (6.25)	
	Endocardium	1 (1.45)	1 (2.7)	0 (0)	
	Pace	1 (1.45)	1 (2.7)	0 (0)	
	No valve involvement	14 (20.29)	5 (13.51)	9 (28.13)	
Findings	Cardiopulmonary	21 (30.43)	11 (29.73)	10 (31.25)	0.89
	Musculoskeletal	1 (1.45)	1 (2.7)	0 (0)	1
	Gastrointestinal	6 (8.7)	3 (8.11)	3 (9.38)	0.85
	Neurological	18 (26.09)	7 (18.92)	11 (34.38)	0.14
	Shock	11 (15.94)	3 (8.11)	8 (25)	0.05
	Splenomegaly	4 (5.8)	4 (10.81)	0 (0)	0.11
	Rash	4 (5.8)	3 (8.11)	1 (3.13)	0.6
Complications		56 (81.16)	26 (70.27)	30 (93.75)	**0.01**
	Neurological	21 (30.43)	7 (18.92)	14 (43.75)	**0.02**
	Embolic	39 (56.52)	16 (43.24)	23 (71.88)	**0.01**
	Heart	15 (21.74)	9 (24.32)	6 (18.75)	0.57

Table 2. Comparison of laboratory parameters in patients with infective endocarditis

Parameters	Survived median (IQR)	Deceased median (IQR)	p
Leukocytes (mm^3)	11500 (8100-15720)	15685 (9765-19290)	0.07
Erythrocyte sedimentation rate (mm/h)	60 (45-88)	56 (23-84)	0.43
C-reactive protein (mg/L)	155 (60-234)	177 (95.5-264.5)	0.56
Procalcitonin (ng/ml)	1.51 (0.37-5.24)	2.47 (0.69-9.74)	0.21
Calcium (mg/dL)	9.02 (8.7-9.4)	9 (8.74-9.28)	0.75
Phosphorus (mg/dL)	3.5 (3.2-4.4)	4.1 (3.2-4.9)	0.32
Urea	52 (28-100)	97 (72-124.5)	**0.001**

Table 3. Comparison of microbiological agents in patients with infective endocarditis

Factors	In total	Survived	Deceased	p
MRSA, n (%)	14 (20.29)	4 (10.81)	10 (31.25)	**0.03**
MSSA, n (%)	22 (31.88)	12 (32.43)	10 (31.25)	0.91
MRCoNS, n (%)	7 (10.14)	2 (5.41)	5 (15.63)	0.23
MSCoNS, n (%)	1 (1.45)	0 (0)	1 (3.13)	0.46
Staphylococcus lugdunensis, n (%)	1 (1.45)	1 (2.7)	0 (0)	1
Streptococcus viridans, n (%)	1 (1.45)	1 (2.7)	0 (0)	1
Streptococcus anginosus, n (%)	1 (1.45)	1 (2.7)	0 (0)	1
Streptococcus mitis/oralis, n (%)	3 (4.35)	3 (8.11)	0 (0)	0.24
Enterococcus feacalis, n (%)	5 (7.25)	3 (8.11)	2 (6.25)	1
Enterococcus faecium, n (%)	2 (2.90)	2 (5.41)	0 (0)	0.49
Enterococcus durans, n (%)	1 (1.45)	0 (0)	1 (3.13)	0.46
Candida parapsilosis, n (%)	1 (1.45)	0 (0)	1 (3.13)	0.46
Klebsiella pneumoniae, n (%)	1 (1.45)	1 (2.7)	0 (0)	1
Pseudomonas aeruginosa, n (%)	1 (1.45)	1 (2.7)	0 (0)	1
Brucella spp., n (%)	1 (1.45)	1 (2.7)	0 (0)	1
Culture negative, n (%)	7 (10.14)	5 (13.51)	2 (6.25)	0.43

MRSA: Methicillin-resistant *S. aureus*, MSSA: Methicillin-sensitive *S. aureus*, MRCoNS: Methicillin-resistant coagulase-negative staphylococci, MSCoNS: Methicillin-sensitive coagulase-negative staphylococci.
†: Independent samples T-test, *: Chi-square test, ¶: Fisher's exact test, µ: Mann-Whitney U test.

Table 4. Univariate analysis for in-hospital mortality in patients with infective endocarditis

	Univariate Analysis		
Parameters	**OR**	**95% CI**	**p**
Age	1.06	1.02-1.1	**0.002**
Prosthetic valve	10.08	1.17-87.1	**0.036**
Chronic kidney disease	2.74	1.03-7.27	**0.043**
Complications	6.35	1.29-31.29	**0.023**
MRSA	3.75	1.04-13.47	**0.043**
Comorbidity	3.79	1.09-13.18	**0.036**

MRSA: Methicillin-resistant *S. aureus*.

Table 5. Multivariate regression models for in-hospital mortality in patients with infective endocarditis

	Multivariate Model 1		
Parameters	**OR**	**95% CI**	**p**
Age	1.06	1.01-1.11	0.027
Prosthetic valve	8.96	0.79-101.43	0.077
Chronic kidney disease	1.88	0.57-6.17	0.297
Complications	4.24	0.7-25.61	0.115
MRSA	3.09	0.68-14.07	0.144
Comorbidity	0.63	0.11-3.6	0.602
	Multivariate Model 2		
Parameters	**OR**	**95% CI**	**p**
Prosthetic valve	12.17	1.18-125.67	0.036
Complications	6.18	1.08-35.24	0.040
MRSA	3.40	0.87-13.37	0.080

Model 1: Age, prosthetic valve, chronic kidney disease, complication, MRSA, comorbidity.
Model 2: Prosthetic valve, chronic kidney disease, complication, MRSA, comorbidity.
MRSA: Methicillin-resistant *S. aureus*.

(OR= 12.17, CI= 1.18-125.67, p= 0.036), and presence of complications (OR= 6.18, CI= 1.08-35.24, p= 0.040) were independent predictors for in-hospital mortality (Table 5).

DISCUSSION

In this study, we evaluated 69 patients with infective endocarditis in a tertiary care university hospital and found that the in-hospital mortality rate was 46.4%. Additionally, older age, the presence of a prosthetic valve, and the presence of complications were independently associated with in-hospital mortality.

In-hospital mortality rates in infective endocarditis can vary up to 50% depending on patient characteristics[7-10]. In the study by Chaudry et al., the mortality rate was 22%[11]. Similarly, Lauridsen et al. reported an in-hospital mortality rate of 16%[6]. The high mortality rate (46.4%) in our study may be related to the increased median age and higher prevalence of comorbid conditions. Additionally, the complication rate in our patient group was high. In the present study, the complication rate (at least one or more) among patients with infective endocarditis was 81.2%. The most common type of complication was embolic events, with a rate of 56.5%. Embolic events may occur both before clinical presentation and after treatment[12]. Therefore, patients with arterial embolization should be examined for evidence of infective endocarditis.

S. aureus was the leading causative agent in our study, with a rate of 52.2%, consistent with findings from other studies[13]. Fowler et al. revealed that MRSA was associated with complications and in-hospital mortality[14]. They found that the in-hospital mortality rate was 22.4% among patients with MRSA, compared to 14.6% among those without MRSA. In addition, increased age, stroke, and persistent bacteremia were identified as independent factors for in-hospital mortality. Lauridsen et al. found that age, chronic dialysis, valve predisposition, stroke, persisting bacteremia, perforation, and abscess were associated with increased risk for in-hospital mortality[6]. In the study of Chu et al., diabetes mellitus, *S. aureus*, and embolism were independent predictors for in-hospital mortality[7].

Spies et al. reported that the in-hospital mortality was 52% in dialysis-dependent patients[10]. In the study of Zolfaghari, the in-hospital mortality rate was significantly higher in dialysis-dependent patients than in patients without chronic kidney disease (41.2% vs. 14.3%)[15]. However, no significant difference in mortality was found between patients without chronic kidney disease

(40.0%), those with chronic kidney disease (72.7%), and dialysis-dependent patients (43.5%) in our study (p= 0.156).

Clinicians should be aware of the need for prompt action because chronic dialysis represents a growing population of patients with infective endocarditis and poses a diagnostic and therapeutic challenge[16,17]. Hemodialysis is a life-sustaining treatment method for patients with chronic kidney disease. However, the risk of developing infective endocarditis may be increased in patients with chronic kidney disease and those undergoing chronic hemodialysis. The number of patients with end-stage renal disease and renal replacement therapy is increasing both in Türkiye and in the world. The frequency of infective endocarditis is 50-200 times higher in chronic kidney disease. It is known that hemodialysis procedures increase the susceptibility to infective endocarditis through multiple mechanisms. Hemodialysis patients are at high risk for infective endocarditis due to impaired immune response, frequent intravenous interventions, and calcifications in the vascular structure[18]. Therefore, we encountered an increased prevalence of chronic kidney disease (49.3%) and chronic hemodialysis (33.3%) in patients with infective endocarditis.

Limitations

This study had some strengths. First, we could evaluate various factors such as demographic features, clinical characteristics, laboratory parameters, echocardiography findings, and etiological agents. Second, we performed multivariate models to determine independent variables on the in-hospital mortality in patients with infective endocarditis. However, we had several limitations. First, this study was conducted in a single center. Second, due to its retrospective nature, we were unable to obtain some data including mortality as a dependent variable. Furthermore, twenty patients were transferred to another hospital and were considered missing. Third, our sample size was relatively small. Therefore, prospective studies with larger populations are needed.

CONCLUSION

Infective endocarditis is a complex and dreadful disease, with nearly half of the patients succumbing to it. Although chronic kidney disease was the most common comorbidity among patients with infective endocarditis, neither chronic kidney disease nor chronic dialysis was independently associated with in-hospital mortality. Older adults with complicated prosthetic valve endocarditis should be prioritized as high-risk targets in the management of infective endocarditis.

ETHICS COMMITTEE APPROVAL

This study was approved by the Haseki Training and Research Hospital Scientific Research Ethics Committee (Decision no: 49-2024, Date: 27.06.2024).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: GT, SS, CGG

Analysis/Interpretation: SS, GT, US, BÇ, FP, EB

Data Collection or Processing: ÇY, CGG, GT

Writing: GT, SS, KGG, ÇY, CGG

Review and Correction: All of authors

Final Approval: All of authors

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