ORIGINAL RESEARCH

Outcomes of Hospitalized Patients with Infective Endocarditis: A Tertiary Center Experience

Enfektif Endokardit Bulgularımız: Üçüncü Basamak Merkez Deneyimi

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Abstract

Objective: The purpose of this study is to report our experience with a comprehensive view of patients hospitalized in tertiary level center with a diagnosis of infective endocarditis (IE).

Method: Medical records of patients who were hospitalized with a diagnosis of IE between January 2017 and December 2019 were retrospectively reviewed by using hospital database. Two groups were generated as survivors and non-survivors. Surgical intervention, occurrence of complications, and in-hospital and 30-day mortality data were noted.

Results: A total of 53 patients (58.5% male) were included in this single-center retrospective study. Native valve endocarditis was more common (86.8%) and located in mitral position. Seven patients had mechanical prosthetic valve infection, those were also in mitral position. Most of the patients (92.4%) had vegetation size greater than 10 mm. Thirty-one patients (58.5%) had culture negative endocarditis while *Staphylococcus aureus* was the most common (9.4%) cultured organism. In-hospital or 30-day mortality was found 35.8%. The rate of embolism was 45.3%. Risk factors associated with mortality included advanced age, lower body mass index, being in NYHA III/IV status, development of acute renal failure and embolic phenomenon, septic shock, congestive heart failure, and presence of tricuspid regurgitation higher than moderate degree. Early valve surgery seems to improve the prognosis of IE according to our findings.

Conclusion: Advanced age, lower BMI, being in NYHA III/IV status, previous history of hypertension, presence of tricuspid valve regurgitation higher than moderate degree, occurrence of acute renal failure, embolic phenomenon, septic shock, and congestive heart failure was found as risk factors for mortality. Early valve surgery may improve prognosis of IE according to our study.

Keywords: Heart valve disease, infective endocarditis, prognosis

Öz

Amaç: Bu çalışmada, Türkiye'de üçüncü basamak bir hastanede enfektif endokardit (EE) tanısı ile yatan ve tedavi gören hastaların kapsamlı değerlendirilmesi ve mortalite ilişkili faktörlerin ortaya çıkarılması amaçlanmıştır.

Yöntem: EE tanısı ile Ocak 2017 ve Aralık 2019 tarihleri arasında hastanemize yatırılan hastaların tıbbi kayıtları hastane veri tabanı kullanılarak retrospektif olarak incelendi. Ölen ve sağ kalan olarak iki grup oluşturularak cerrahi müdahale, komplikasyon oluşumu, hastane içi ve 30 günlük mortalite verileri kaydedildi.

Bulgular: Tek merkezli bu çalışmaya retrospektif olarak toplam 53 hasta (%58,5 erkek) dahil edildi. Hastaların %86,8'i doğal kapak endokarditi olup en sık tutulan kapak mitral kapaktı. Yedi hastada protez kapak enfeksiyonu saptanmış olup, bunlar da mitral lokalizasyondaydı. Hastaların %92,4'ünde 10 mm'den büyük vejetasyon gözlendi. Otuz bir hastada (%58,5) kültür negatif endokardit bulunurken, üreme olduğunda en sık izole edilen mikroorganizma *Staphylococcus aureus* idi. Hastane içi veya 30 günlük mortalite oranı %35,8 ve emboli oranı %45,3 idi. Mortalite ile ilişkili risk faktörleri ileri yaş, düşük vücut kitle indeksi, NYHA III/IV statüsünde olma, akut böbrek yetmezliği, embolik olay gelişimi, septik şok, konjestif kalp yetmezliği ve orta dereceden fazla triküspit yetersizliği olarak tespit edildi.

Sonuç: İleri yaş, düşük vücut kitle indeksi, NYHA III/IV statüsünde olmak, önceden hipertansiyon öyküsü, orta dereceden fazla triküspit kapak yetersizliği varlığı, akut böbrek yetmezliği oluşumu, embolik olay, septik şok ve konjestif kalp yetmezliği mortalite için risk faktörleri olarak saptandı. Çalışmamıza göre erken kapak cerrahisi uygulanan hastalarda mortalite daha düşüktür ve erken cerrahi EE'nin prognozunu iyileştiriyor gibi görünmektedir.

Anahtar kelimeler: Enfektif endokardit, kalp kapak hastalığı, prognoz

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Introduction

Despite advances in diagnosis and medical/surgical treatment in cardiology, infective endocarditis (IE) is still a life-threatening condition with a mortality rate approaching 34% (1). With the decreasing incidence of rheumatic fever and advances in interventional valvular heart disease therapies, the epidemiology of IE has shifted from younger patients with rheumatic fever to older subjects with multiple diseases. While the percentage of patients newly diagnosed with IE remained the same as in the past two decades (2), ten new cases of IE were reported per 100,000 population year in the Western population (3).

Heart failure, systemic embolization, cardiogenic shock and stroke, disseminated infection, abscess formation and arrhythmias including complete heart block are well-defined complications and the type of infecting pathogen, duration of infectious state prior to therapy, accompanying comorbidities, the localization and size, and mobility of vegetation are known risk factors for complications. Antibiotic regimen, timing of surgery and management of complications have been explained in detail in the European Society of Cardiology Guidelines (4).

In this study, we aimed to describe our experience with a comprehensive view of patients hospitalized in tertiary level center with a diagnosis of IE. The primary outcome of this study was to evaluate factors associated with in-hospital and 30-day mortality in patients hospitalized with IE.

Materials and Methods

Patients who were diagnosed and hospitalized with the International Classification of Diseases code for IE (I33.0) in our tertiary center hospital between January 2017 and December 2019 were included in this retrospective study. Seventy-seven patients matched with this code were evaluated and diagnosis was made based on Duke's criteria as defined in the current guidelines (4) and 53 patients (58.5% male) who meet Duke's criteria were included. The remaining 24 patients were excluded due to lack of echocardiographic findings or unproven minor criterion. Medical records were reviewed for patients' demographic information, medical history, predisposing conditions (intravenous drug use, poor dental health, immunocompromised condition due to organ transplantation or autoimmune disease etc. and rheumatic heart disease), laboratory results, blood culture findings and clinical characteristics of endocarditis by using hospital database. Antibiotic regimen decision and timing of

surgery were applied according to current guidelines in our tertiary center hospital. Surgical intervention, occurrence of complications, and in-hospital and 30-day mortality data were noted. Echocardiography views were reviewed to define the location, size, and mobility of vegetation.

This study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital was obtained (date: 05/07/2022, number: 2022/07/03/003). Human Studies and Research Committee of our institution and patient consent was waived accordingly.

Statistical Analysis

The Statistical Package for the Social Sciences 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Categorical data were expressed as number (n) and percentages (%). Continuous variables were expressed as mean ± standard deviation. Variables having linear correlation were evaluated by using the Pearson's correlation test and non-linear variables were evaluated by using the Spearman's correlation test. Independent variables of in-hospital and 30-day mortality were identified by using binary logistic regression analysis. The groups were compared in terms of in-hospital and 30-day mortality occurrence by the Mann-Whitney U test. The chi-square test was used to assess differences in categorical variables between groups. Significance was presumed at a 2-sided $p<0.05$.

Results

Clinical Findings

The patients with a matched code for IE were reassessed for the Duke's criteria (5) and 53 patients (58.5% male) were included in this single-center retrospective study. The mean age of patients was 56.9±16.7 years and the mean body mass index was 25.7±4.3. Diabetes mellitus (DM) was present in 24.5% of patients while hypertension (HT) was in 39.6%. There were 3 patients (5.7%) with a diagnosis of coronary artery disease (CAD), 2 (3.8%) with chronic obstructive pulmonary disease (COPD), and 2 (3.8%) with immunocompromised situation. In the study group, 5.7% of patients were current smokers. Nine (17%) patients were in atrial fibrillation rhythm. When the patients were evaluated according to the symptoms at presentation, fever (94.3%) and chills (94.3%) were the most common symptoms, followed by dyspnea (92.5%), palpitation (79.2%), syncope (26.4%), and chest pain (11.3%). Most of the patients (75.5%) were in NYHA III/IV class (Table 1).

Table 1. Demographic, clinical data of patients and complications during follow-up				
Variables	All patients (n=53)	Survivors (n=34)	Non-survivors (n=19)	p
Age , years	56.9±16.7	53.3±14.9	63.6±18.1	**0.031**
Male, n (%)	31 (58.5)	21 (48.4)	10 (52.6)	0.570
Body mass index (kg/m²)	25.7±4.3	27.1±4.3	23.2±3.03	**0.001**
Smoking, n (%)	3 (5.7)	1 (33.4)	2 (66.6)	0.290
Chronic obstructive pulmonary disease, n (%)	2 (3.8)	-	2 (100)	0.124
Coronary artery disease, n (%)	3 (5.7)	2 (66.6)	1 (33.4)	0.710
Hypertension, n (%)	21 (39.6)	9 (42.8)	12 (57.1)	**0.018**
Diabetes mellitus, n (%)	13 (24.5)	7 (53.8)	6 (46.2)	0.285
Hyperlipidemia, n (%)	1 (1.9)	1 (100)	-	0.642
Chronic renal failure, n (%)	8 (15.1)	3 (37.5)	5 (62.5)	0.098
Immunsupresive condition, n (%)	2 (3.8)	-	2 (100)	0.124
Malignancy, n (%)	1 (1.9)	-	1 (100)	0.358
Atrial fibrillation, n (%)	9 (17)	4 (44.4)	5 (55.5)	0.165
Symptoms at presentation				
Chest pain, n (%)	6 (11.3)	4 (66.6)	2 (33.3)	0.634
Dyspnea, n (%)	49 (92.5)	31 (63.2)	18 (36.7)	0.547
NYHA III/IV, n (%)	40 (75.5)	21 (51.5)	19 (47.5)	**0.001**
Paipitation, n (%)	42 (79.2)	24 (51.2)	18 (42.8)	**0.036**
Fever, n (%)	50 (94.3)	31 (62)	19 (38)	0.255
Dizziness, n (%)	50 (94.3)	31 (62)	19 (38)	0.255
Syncope, n (%)	14 (26.4)	6 (42.8)	8 (57.1)	0.055
Complications				
Leaflet perforation, n (%)	10 (18.9)	8 (80)	2 (20)	0.217
Chordal rupture, n (%)	10 (18.9)	7 (70)	3 (30)	0.484
Pseudoanevrisma	6 (11.3)	6 (100)	-	**0.059**
Severe valvular dysfunction	48 (90.6)	29 (60.4)	19 (39.6)	**0.097**
Major embolic events	24 (45.3)	11 (45.8)	13 (54.2)	0.012
Renal	4 (7.5)	4 (100)	-	0.158
Cerebral	14 (26.4)	5 (35.7)	9 (64.3)	0.013
Peripheric extremity	3 (5.7)	3 (100)	-	0.250
Splenic	5 (9.4)	3 (60)	2 (40)	0.596
Acute renal failure, n (%)	10 (18.8)	2 (20)	8 (80)	**0.002**
Acute heart failure, n (%)	17 (32.07)	2 (11.7)	15 (88.2)	**<0.0001**
Septic shock, n (%)	18 (33.9)	2 (11.1)	16 (88.8)	**<0.0001**
Total length of hospital stay, n (days)	33 (22.5-84)	36.2±10.6	25.6±19.5	**0.014**
Surgery, n (%)	37 (69.8)	30 (81.1)	7 (18.9)	**<0.0001**

NYHA: New York Heart Association

Laboratory and Echocardiographic Findings

With regards to echocardiographic data, 15 patients had vegetations greater than 20 mm, 34 patients had vegetations between 10 and 20 mm in diameter and 4 had less than 10 mm. Native valve endocarditis was more common (86.8%) and vegetations were in the mitral valve position in 34 (64.2%) patients, aortic valve position in 25 (47.2%) patients, and both aortic and mitral valve positions in 9 of

these patients. Seven patients have mechanical prosthetic valve infection, 6 of them were localized in mitral position and 1 patient had a bioprosthetic valve infection that was also in mitral position (Table 2).

A total of 22 (41.5%) patients had a positive blood culture pre-operatively, with *Staphylococcus aureus* being the most cultured organism (15.1%). Coagulase negative *Staphylococci* was cultured in 5 (9.4%) and group B

Streptococcus in 4 patients (7.5%). Thirty-one patients (58.5%) had culture negative endocarditis (Table 2). In-hospital or 30-day mortality was found in 35.8% (19 patients). In addition, the rate of acute renal failure was 18.8%, the rate of acute decompensated heart failure was 32.07%, and the rate of septic shock was 33.9% in this study. The localization of embolization was defined according to clinical and radiological findings. A total of 24 patients (45.3%) experienced major embolic events; fourteen patients experienced cerebral embolism while 3 patients had peripheral arterial embolism, 5 patients had splenic embolism and 4 patients had renal embolism (Table 1).

Table 2. Laboratory and echocardiographic data of patients

Variables	All patients (n=53)	Survivors (n=34)	Non-survivors (n=19)	p
Laboratory findings				
Haemoglobin (g/dL)	9.5±1.6	10.02±1.7	8.68±1.25	**0.005**
Platelet (10³/µL)	250±139	292±115	176±150	**0.003**
White blood cell (10³/µL)	11.7±4.6	11.4±4.9	12.3±4.2	0.526
Neutrophil (10³/µL)	6.01±5.5	6.7±3.03	6.8±3.5	0.798
Lymphocyte (10³/µL)	1.06 (0.12-11.92)	0.87 (0.55-7.63)	1.06 (0.12-11.92)	0.675
Creatinine (mg/dL)	0.9 (0.43-6.85)	0.92 (0.49-5.48)	0.91 (0.43-6.85)	0.697
Glomerular filtration rate (mL/dk/1.73 m²)	95±29.02	88.8±28.7	85.9±30.3	0.375
C-reactive protein (mg/L)	107.8±74.9	86.9±58.8	145.2±86.9	**0.005**
NT-pro-BNP (ng/mL)	1473.3 (124-35000)	480 (124-18400)	19800 (9602-35000)	**<0.0001**
Erytrocite sedimentation rate	61.6±29.7	61.5±28.9	62±31.7	0.951
Procalcitonin (ng/mL)	7.58 (0.64-36.9)	0.84 (0.73-36.9)	13.2 (0.92-33.1)	**0.001**
Troponin-I (pg/mL)	38 (4-3963)	32.6 (41.-709)	57.6 (16-3963)	0.084
Blood culture analysis				
Staphylococcus aureus	8 (15.1)	2	6	
Coagulase negative *Staphyloccus*	5 (9.4)	3	2	
Streptococcus mutans	4 (7.5)	4	-	
HACEK	1 (1.9)	-	1	
Enterococcus foecallis	2 (3.8)	1	1	
Candida albicans	1 (1.9)	-	1	
Brucellacae	1 (1.9)	1	-	
Culture negative	31 (58.5)	22	9	
Echocardiographic findings				
Ejection fraction, (%)	59.1±6.7	58.2±6.7	57.8±6.9	0.862
Left ventricular end-diastolic diameter, (mm)	49.2±5.7	50.8±5.9	50.1±5.6	0.646
Left ventricular end-systolic diameter, (mm)	31.7±6.1	34.5±6.1	34.7±6.2	0.904
Left atrium, (mm)	42.4±5.1	42.2±5.6	42.7±4.2	0.736
TAPSE, (mm)	18.1±3.2	18±3.6	17.7±2.3	0.734
Effected valves, n (%)				
Native valves	46 (86.8)	30 (65.2)	16 (34.7)	0.491
Prosthetic valves	7 (13.2)			
Metalic	6 (11.3)		3 (50)	0.491
Bioprothesis	1 (1.9)	3 (50)	1 (100)	0.358
Aortic	25 (47.2)	–	9 (36)	0.604
Mitral	34 (64.2)		12 (35.3)	0.570
Aortic and mitral	13 (24.5)	16 (64)	5 (38.5)	0.536
Tricuspide	3 (5.6)	22 (64.7)	3 (100)	0.765
		8 (61.5)		
		–		
Vegetation area, (mm²)	137 (15-686)	118 (15-686)	167 (44.1-478)	0.525
Tricuspide regurgitation (>2)	20 (37.7)	8 (40)	12 (60)	**0.007**

HACEK: *Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella* corrodens, and *Kingella* species; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; TAPSE: Tricuspid annular plane systolic excursion

Findings According to Mortality

We further divided 53 patients into survivor and non-survivor groups. Both groups were similar in terms of gender, smoking, DM, immunocompromised condition, COPD, CAD, CRF, and history of malignancy. However, age and HT were significantly higher in the non-survivor group (63.6±18.1 vs. 53.3±14.9, p=0.031; 57.1% vs. 42.8%, p=0.018, respectively). Moreover, body mass index was significantly lower in the non-survivor group (23.2±3.03 vs. 27.1±4.3, p=0.001). The presence of tricuspid regurgitation higher than moderate degree was also higher in the non-survivor group (60% vs. 40%; p=0.007). In terms of laboratory markers, NT-pro-BNP [19800 (9602-35000) vs. 480 (124-18400); p<0.0001], C-reactive protein (CRP) (145.2±86.9 vs. 86.9±58.8; p=0.005), procalcitonin [13.2 (0.92-33.1) vs. 0.84 (0.73-36.9); p=0.001] were significantly higher and hemoglobin (8.68±1.25 vs. 10.02±1.7; p=0.005), platelet counts (176718.4±150446.7 vs. 292344.1±115628; p=0.003) were significantly lower in the non-survivor group. Furthermore, acute renal failure (80% vs. 20%, p=0.002), major embolic events (54.2% vs. 45.8%, p=0.012), decompensated heart failure (88.2% vs. 11.7%, p<0.0001), and septic shock (88.8% vs. 11.1%, p<0.0001) occurred more common in the non-survivor group. When major embolic events were detailed, it was observed that cerebral embolism (64.3% vs. 35.7%, p=0.013) was significantly higher. According to treatment data, 81.1% of patients in the survivors and 18.9% of non-survivors underwent surgery (p<0.0001). Early surgery was performed within 1-6 days of hospitalization to prevent embolism, heart failure and uncontrolled infection. Patients with high risk of surgery (e.g., high intracranial bleeding risk in patients with cerebral embolism or patients in septic shock) did not undergo early surgery. Laboratory and clinical data of the groups are presented in detail in Tables 1, 2.

Discussion

This study was designed to evaluate hospitalized patients with a diagnosis of IE in our institution. Several features were identified that are compatible with previous literature. Risk factors associated with mortality were advanced age, lower BMI, being in NYHA III/IV status, previous history of HT, occurrence of acute renal failure, embolic phenomenon (especially cerebral embolism), septic shock, congestive heart failure, and presence of tricuspid valve regurgitation higher than moderate degree. Regarding laboratory markers, higher NT-proBNP, CRP, procalcitonin values and lower hemoglobin and platelet counts were detected as

associated factors with mortality. Early valve surgery may improve the prognosis of IE according to our findings.

According to blood culture results, *Staphylococcus aureus* was the most common cultured organism (15.1%). Our patients were usually referred from other clinics and the blood cultures were taken under antibiotic treatment. This resulted as high prevalence (58.5%) of negative blood culture in our study. *Staphylococcus aureus* is also the most common organism in IE patients in the literature; however, microbiologic shift to *Streptococcus* and HACEK (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens* and *Kingella*) organisms was reported (6,7).

There are conflicting data regarding early surgery in the literature. In a randomized study, early surgery was shown to significantly reduce morbidity and embolic events especially in patients with large left-sided lesions (>10 mm), whereas some studies have failed to show survival benefit of early surgery with native valve endocarditis (8-10). Another indication for early surgery is uncontrolled infection. This was supported by several retrospective cohort studies showing that locally aggressive infection was associated with a higher mortality rate (11,12). Early surgery is recommended for patients with heart failure and high-risk lesions to prevent embolization and for those with uncontrolled infection according to current guidelines (4). The presence of congestive heart failure has been defined as the most consistent predictor of mortality in previous studies (13,14). Congestive heart failure was found to be an independent predictor of mortality in our study, as well. In our analysis, mortality was significantly lower in patients who underwent surgery in the acute phase of endocarditis. The incidence of embolic events was 33% and the brain was the most common embolism site (15). Similarly, embolic events were found to be significantly associated with mortality; however, they were not defined as independent predictors of mortality. We detected a higher rate of embolism (45.3%) and the most common embolism site was the brain due to the impairment in the middle cerebral artery and its branches. Haemorrhagic transformation occurred in 5 patients (35.7%) and surgery was postponed. The high rate of embolic complications may be explained via relatively larger vegetation size, since 92.4% of patients had a vegetation size greater than 10 mm according to our echocardiographic findings. History of hypertension, presence of syncope, occurrence of congestive heart failure during the disease course, higher erythrocyte sedimentation rate and procalcitonin levels

were documented to be associated risk factors with embolic events.

Patients with comorbidities, history of valvular heart disease or mechanical heart valve, being underwent more invasive medical procedures, less likely to undergo heart surgery and advanced age have been shown to be independent risk factors for mortality in IE (3,16,17). Advanced age was detected as a risk factor for mortality. Although, an overestimation of male gender has been reported (18), the risk of acquiring fatal IE was found similar in both genders in our study

Study Limitations

This analysis should be interpreted in terms of its retrospective design, low number of patients, and lack of long-term follow-up. However, controlled studies are not applicable due to the nature of the disease. Further statistical analyses were not performed due to small sample size and lower number of patients in subgroups. It would be more informative to compare two groups with the same level disease to define predictors of mortality; however, this could not be applied due to the small sample size.

Conclusion

The mortality and morbidity of IE remains high despite advances in treatment. Risk factors associated with mortality according to our small study group were advanced age, lower BMI, being in NYHA III/IV status, previous history of HT, presence of tricuspid valve regurgitation higher than moderate degree, occurrence of acute renal failure, embolic phenomenon (especially cerebral embolism), septic shock, and congestive heart failure. Regarding laboratory markers, higher NT-proBNP, CRP, procalcitonin values and lower hemoglobin and platelet counts were detected as the factors associated with mortality. Early valve surgery may improve the prognosis of IE according to our study.

Highlights

• The morbidity/mortality associated with IE is still high.

• Since most of the patients were referred from other clinics, clinical suspicion is essential.

• Early surgery seems to improve prognosis.

Ethics

Ethics Committee Approval: This study was approved by Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital was obtained (date: 05/07/2022, number: 2022/07/03/003).

Informed Consent: Patient consent waived due to retrospective design.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: S.Ö., E.D., İ.Ş., E.O., Design: S.Ö., E.D., İ.Ş., E.O., Data Collection or Processing: S.Ö., E.D., O.İ., E.H., E.M.F., Analysis or Interpretation: S.Ö., E.D., O.İ., E.H., E.M.F., Literature Search: S.Ö., E.D., O.İ., E.H., E.M.F., Writing: S.Ö., E.D., İ.Ş., E.O.

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