RESEARCH ARTICLE / *Araştırma Makalesi*

Clinical and Laboratory Characteristics of Patients with Infective Endocarditis: A Single-Center Experience

Enfektif Endokardit Hastalarının Klinik ve Laboratuvar Özellikleri: Tek Merkez Deneyimi

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Öz

Objective	This study aimed to evaluate the clinical presentations, outcomes, and changes over 8 years period of infective endocarditis (IE) patients in a tertiary hospital in Turkey and to identify predictors of mortality.
Materials and Methods	All adult patients who were hospitalized with a diagnosis of definite IE were included in the study. The data were analyzed both collectively and separately in two consecutive four-year periods i.e. 2010-2013 and 2014-2017.
Results	There were 72 IE cases in the study. Male/female ratio was 1.57:1 (44 males,28 females). The mean age of the patients was 48.5±17.6 years. Staphylococci were the most common agents (44%). Independent predictors of mortality were heart failure, the invasive procedure before IE, and lower platelet level. Increased invasive procedures before IE and enterococcal endocarditis were found significantly to be higher during the last period (2014-2017).
Conclusion	IE is still a serious and deadly disease in the 21st century. Our data indicate that invasive procedures have been increasing before IE and this increase with associated poor prognosis.
Keywords	Endocarditis; epidemiology; mortality.

Abstract

Amaç	*Bu çalışmada, Türkiye'de üçüncü basamak bir hastanede yatan enfektif endokardit (EE) tanılı hastaların klinik özelliklerini, sonuçlarını ve sekiz yıllık dönemdeki değişiklikleri değerlendirmek ve mortalite risk faktörlerini belirlemek amaçlandı.*
Gereç ve Yöntemle	*Çalışmaya kesin EE tanısıyla yatırılarak takip edilen tüm erişkin hastalar dahil edildi. Çalışma verileri toplu şekilde ve iki ardışık dört yıllık dönem şeklinde (2010-2013 ve 2014-2017) analiz edildi.*
Bulgular	*Çalışmada 72 EE hastası mevcuttu. Erkek/kadın cinsiyet oranı 1,57:1 (44 erkek, 28 kadın) idi. Hastaların ortalama yaşı 48,5±17,6 yıldı. Stafilokoklar en yaygın etken olarak bulundu (%44). Kalp yetmezliği, EE öncesi girişimsel işlem varlığı ve düşük trombosit seviyesi, mortalite için bağımsız risk faktörü olarak bulundu. EE öncesi artan girişimsel işlem varlığı ve enterokokal endokardit, son dönemde (2014-2017) anlamlı olarak daha yüksek bulundu.*
Sonuç	*EE, 21. yüzyılda hala ciddi ve ölümcül bir hastalıktır. Verilerimiz, enfektif endokardit tanısı öncesinde girişimsel işlem varlığının artmakta olduğunu ve bu durumun kötü prognozla ilişkili olduğunu göstermektedir.*
Anahtar Kelimeler	*Endokardit; epidemiyoloji; mortalite.*

INTRODUCTION

Infective endocarditis (IE) is a rare but severe infectious disease with increased incidence in recent years.[1,2] IE is related to high costs because of prolonged hospitalization and can require surgical improvement. Risk factors for IE clinical spectrum have changed in the last decades with increased health care procedures; including intracardiac devices, central venous catheterization, hemodialysis.[3-5] Several studies have noted an increase in the proportion of IE caused by staphylococcal species.[4,6]

Although blood culture is a major criterion for diagnosis for IE, culture-negative endocarditis remains an important clinical situation.[2,7] The current in-hospital mortality rate for IE is 15-30%, with one-year mortality approaching 40%.[1,2,8-11] Despite advances in diagnosis (including imaging techniques such as cardiac CT, F-FDG PET/CT, or leucocytes labeled SPECT/CT and treatment, mortality and several complications rates are still high.[2]

This study aimed to evaluate the clinical presentations, etiology, echocardiographic findings, outcomes, and changes in characteristics of IE patients in a tertiary hospital in Turkey over 8 years and to identify predictors of mortality.

MATERIALS and METHODS

The ethics committee of the Ankara Numune Training and Research Hospital approved this study design (confirmation date and number: 29.03.2017, 1320/2017). This study was conducted by the principles of the Declaration of Helsinki.

Study design

This study is a retrospective observational cohort study. All adult patients (age≥18 years) who were hospitalized in a tertiary hospital in Turkey with a diagnosis of IE between 2010 and 2017 were included in the study.

IE was identified by searching in the main discharge diagnoses of hospitalizations for the ICD-10-CM (International Classification of Diseases) codes I33.0(acute and subacute endocarditis), I38 (endocarditis, valve unspecified), and I33.9(acute endocarditis, unspecified) in the hospital information management system.

Patients' dead or alive information was obtained from the national death notification system data. Information on 12-month-mortality after the time of admission was obtained using each patient's civil registration number. Centralized registration of death based on the individual civil registration number is unique for Turkey and guarantees a 100% follow-up.

The search identified 94 patients with a diagnosis of IE. All of these patients' clinical records were reviewed. Patients with definite IE according to the modified Duke criteria were included in the study. Twenty-two patients who did not meet the inclusion criteria and/or whose all of the data were not available were excluded. Eventually, 72 patients were included in the study.

Data extraction

Each IE patient extracted data into a data collection form. The following variables were recorded for each patient: age, sex, duration of illness before hospital admission (>1 month), previous antibiotic use (within three months before admission), history of recent medical procedures (including dental, gastrointestinal, genitourinary and central venous catheterization, within six months before admission), underlying cardiac predisposition (congenital heart disease (CHD), chronic rheumatic heart disease (CRHD), or degenerative heart diseases), comorbid conditions before IE (diabetes mellitus, chronic renal failure, coronary artery disease, hypertension, chronic obstructive pulmonary disease (COPD), being on chronic haemodialysis, malignancy and/or immunosuppression, intravenous drug use (IVDU), admission complaints, physical investigation findings, laboratory values (blood urea nitrogen, serum creatinine, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bil-

irubin, rheumatoid factor, haemoglobin level, platelet and white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR), urinalysis test (hematuria and proteinuria) at the time of diagnosis), blood culture results, echocardiography findings, antimicrobial treatments, surgical interventions, cardiac and extracardiac complications (neurological events, embolism, congestive heart failure, renal failure) and mortality. Mortality was defined as death occurring within 12 months after diagnosis. These data were primarily analyzed in general. Secondarily, all data were evaluated in two periods of 4-year intervals (2010-2013, 2014-2017).

Statistical analyses

Statistical analyses were done using SPSS for Windows version 17.0 (IBM Corporation, Armonk, NY, USA). Variables were found to be significant ($p<0.05$). The distribution of continuous variables was investigated with the Kolmogorov–Smirnov test. The significance of the difference between the mean values of the groups was assessed by Student's t-test, variables with a non-normal distribution were compared using the Mann–Whitney U test. The Chi-Square and Fisher's tests were used to compare categorical variables. Factors that might be the most determinative factors of mortality were investigated by multivariate stepwise logistic regression analysis. As a result of univariate analysis, all variables identified as $p <0.25$ were taken by a multivariable logistic regression model as candidate risk factors. Also, odds ratios, 95% confidence interval, and wald statistics for each variable were calculated.

RESULTS

During this 8-year study period, a total of 72 IE cases (44 males, 28 females) were identified in the study. The mean age of the patients was 48.5±17.6 years. 47 patients (65%) had one or more comorbidities. The most common underlying condition was hypertension (33.3%). Two patients were intravenous drug users. There was no HIV-positive patient in this cohort. Presence of an invasive procedure within six months before the diagnosis of IE was found in 27 patients (37%). Of all cases, 43 (59.7%) had received a previous course of antibiotic therapy. Forty patients (55.6%) were admitted after one month of the initial signs of illness. Among 72 endocarditis episodes, 25% involved prosthetic valves (n=18) and 8.3% (n=6) were device-related. The most predisposing cardiac risk factors were CRHD (n=27, 37.5%) (Table 1). Seven patients had degenerative and five patients had congenital heart disease. The most frequent symptoms were fever (88.2%), myalgia (79.2%), dyspnea (62.5%) and clinical signs were fever (%90.3), heart murmur (75), and splenomegaly (34.7). The other symptoms and findings of the patients are presented in Table 2.

Echocardiographic features

All patients underwent transthoracic echocardiography (TTE) and half of the patients' transesophageal echocardiography (TOE). Eight patients' TTE's were negative for IE. Seven of these patients had positive TOE. In one patient there was a contraindication therefore TOE couldn't be performed. Valvular involvement was present in 62 patients (86%). Native valve endocarditis was present in 48 patients (67%). Prosthetic valve and pacemaker/ICD endocarditis were seen in 18 patients (25%) and 6 patients (8%), respectively. Mitral (44%) and aortic valves (32%) were infected most commonly. The vegetation was 10 mm more in size in 45 (62.5%) patients and mobile vegetation was observed in 44 (61.1%) patients. Paravalvular complications occurred in 25 (34.7%) patients. Half of the fatal cases had these complications.

Microbiological data and antimicrobial susceptibility

The causative microorganism was identified in 48 patients (66.67%) by positive blood culture. Staphylococci (S. aureus n=14, coagulase-negative staphylococci (CoNS) n=7) were the most isolated microorganisms (n=21, 44%), followed by streptococci (n=12, 25%) and enterococci (n=8, 17.0%). Other microorganisms were identified as two Candida spp., two Brucella spp., and three gram-negative rods (two Pseudomonas spp. and one E.coli). The rate

Table 1. Demographic characteristics and predisposing conditions of patients with infective endocarditis.				
	Patients who survived (n=46)	Patients who died (n=26)	Total patients (n=72)	p-Value
Age, years	45.1±16.2	54.7±18.7	48.5±17.6	**0.025†**
Male gender	27 (58.7%)	17(65.4%)	44 (61.1%)	0.758‡
Total length of hospital stay, days	30 (2-59)	13 (2-78)	25 (2-78)	**0.027¶**
First sign to admission > 1 month	25 (54.3%)	15 (57.7%)	40 (55.6%)	0.978‡
Cardiac risk factors				
Chronic rheumatic heart disease	20 (43.5%)	7 (26.9%)	27 (37.5%)	0.254‡
Prostetic valve endocarditis	10 (21.7%)	8 (30.8%)	18 (25.0%)	0.571‡
Pacemaker/ICD	6 (13.0%)	0 (0.0%)	6 (8.3%)	0.081$
Comorbidities	24 (52.2%)	21 (80.8%)	45 (62.5%)	**0.031‡**
Coronary heart diseases	5 (10.9%)	4 (15.4%)	9 (12.5%)	0.714$
Diabetes mellitus	12 (26.1%)	5 (19.2%)	17 (23.6%)	0.712‡
Hypertension	12 (26.1%)	12 (46.2%)	24 (33.3%)	0.140‡
Chronic renal failure	6 (13.0%)	7 (26.9%)	13 (18.1%)	0.202$
Chronic haemodialysis	4 (8.7%)	5 (19.2%)	9 (12.5%)	0.269$
Malignency and/or immuno-supp-ression	5 (10.9%)	4 (15.4%)	9 (12.5%)	0.714$
Chronic obstructive lung diseases	3 (6.5%)	1 (3.8%)	4 (5.6%)	>0.999$
Previous antibiotic use within 90 days	26 (56.5%)	17 (65.4%)	43 (59.7%)	0.627‡
Invasive procedure within 6-month	13 (28.3%)	14 (53.8%)	27 (37.5%)	0.057‡
Central venous catheterization	7 (15.2%)	8 (30.8%)	15 (20.8%)	0.208‡
† Student's t-test, Data is median±SD. ‡ Chi-Square test, Data are n (%). ¶ Mann Whitney U test, Data are median (min-max). $ Fisher's test, Data are n (%).				

Table 2. Presenting symptoms and clinical findings of patients with infective endocarditis.			
Symptoms	Number (%)	Findings	Number (%)
Fever	65 (90.3)	Fever	62 (86.1)
Myalgia	57 (79.2)	Heart murmur	54 (75)
Artralgia	20 (27.8)	Petechiae	13 (18)
Lack of appetite	30 (41.7)	Splenomegaly	25 (34.7)
Cough	27 (37.5)	Janeway lesion	4 (5.5)
Dispne	46 (62.5)	Osler nodes	10 (13.8)
Weight loss	10 (13.9)	Roth spot	7 (9.7)
Headache	10 (13.9)	Hematuria	39/57 (54.1)
		Elevated C-reactive protein	67 (93)
		Elevated sedimentation rate	60 (83.3)
		Elevated rheumatoid factor	10/18 (13.9)

of methicillin resistance was 28.6% (4/14) for S. aureus strains and 57.1% (4/7) for CoNS strains. Viridians group streptococci were identified in 8 patients, four streptococcus species couldn't be identified. Three streptococcus strains were resistant to penicillin. Among the enterococci, seven species were identified as Enterococcus faecalis. One strain identified as Enterococcus faecium was resistant to ampicillin and vancomycin.

Treatment

The median length of antibiotic treatment was 23.5 (2-45) days. The most commonly used antibiotic was β-lactams ± aminoglycosides (n=34, 47.2%). Then respectively, daptomycin ± aminoglycosides (n=22, 30.6%), vancomycin ± aminoglycosides ± rifampicin (n=11, 15.3%), antifungal agents (n=2), rifampicin ± doxycycline ± ceftriaxone (n=2) and meropenem (n=1) were used.

Although the surgical intervention was decided for 42 patients(58%), only 15 (20.8%) patients underwent surgery due to contraindication or patient rejection.

Outcome

The median length of hospital stay was 25 days (min-max, 2-78). The hospital stay was significantly longer in the non-fatal group (p=0.027). Clinical complications during hospital stay included: embolic events in 35 (48.6% of patients), congestive heart failure in 22 (30.6% of patients), and renal failure in 22 (30.6%) patients.

Overall, 22 patients (30.6%) were discharged with full recovery. A follow-up of 12 patients (16.7%) continued at the outpatient parenteral antibiotic treatment (OPAT) unit. All of these patients were recovered at the end of treatment. Ten of the patients (13.9%) were referred to another hospital because of surgical intervention. The overall hospital mortality rate was 26.4% (19/72), the 12-month mortality rate was 36.1% (26/72). In the univariate analysis, the parameters that increased mortality were older age, presence of the comorbid condition, left-sided endocarditis, renal and heart failure, embolic event, central nervous system (CNS) emboli and/or infarct, lower thrombocyte count, higher urea, creatinine, and bilirubin levels (Table 1, 3 and 4).

As a result of univariate analyses, all variables identified as p <0.25 were taken by a multivariable logistic regression model as candidate risk factors for mortality. The following parameters were included in logistic regression analysis as age, hypertension, chronic renal failure, the invasive procedure before IE, central venous catheterization, WBC, neutrophils, platelets, hemoglobin, CRP, creatinine, AST, total bilirubin, aortic involvement, paravalvular abscess, perforation, rupture of the leaflet, heart failure, renal failure, cranial emboli and/or infarct, lung embolism. Three factors were independently associated with mortality: Heart failure OR: 29.3 (95% CI: 5.9-145.2, p<0.001), invasive procedure before IE OR: 6.8 (95% CI: 1.5-31.3, p=0.013), lower platelet level OR: 1.1 (95% CI: 1.03- 1.20, p=0.003) (Table 5).

Changes in patients characteristics of IE

Patients characteristics were evaluated in two periods; 2010-2013 (n=28) and 2014-2017 (n=44). Invasive procedure before IE (21.4% vs 47.7%) and enterococcal endocarditis (0.0% vs 48.2%) were significantly more prevalent in patients during 2014-2017 period (p=0.046, p=0.019, respectively). All pacemaker lead infections (n=6) occurred during the last period. The first sign to admission after a month rate was higher in the 2014-2017 period (45.5%, 71.4% respectively). But these conditions were not statistically significant (p=0.075 and p=0.055, respectively). Patients' laboratory, echocardiographic findings, and mortality rates were similar between the two periods. Mortality rates were 39.3% and 34.1% respectively.

DISCUSSION

Table 3. Laboratory findings of patients with infective endocarditis.			
	Patients who survived (n=46)	Patients who died (n=26)	Total patients (n=72)
WBC, /μL	10000 (3100-22600)	12700 (2600-49000)	11300 (2600-49000)
Neutrophils, /μL	7750 (600-213300)	10900 (100-112000)	8150 (100-213300)
Thrombocycte count, /μL	240782.6±80161.8	162038.5±122101.7	212347.2±103793.3
Hemoglobin, g/dL	11.2±2.1	10.4±2.6	10.9±2.3
Hematocrit, %	34.0±6.0	32.1±7.7	33.28±6.68
Urea, mg/dL	30.5 (11-232)	80.5 (19-203)	43.5 (11-232)
Creatinine, mg/dL	0.9 (0.3-9.4)	1.9 (0.4-9.0)	1.0 (0.3-9.4)
ALT, U/L	17.5 (3-182)	20.5 (2-267)	19.5 (2-267)
AST, U/L	22 (9-107)	24 (13-169)	22.5 (9-169)
Total bilirubin, mg/dL	0.7 (0.3-2.5)	1.1 (0.3-10.1)	0.7 (0.3-10.1)
CRP, mg/L	62 (2-361)	101 (6-343)	73 (2-361)
Sedimentation, mm/h	48.2±24.8	42.8±35.3	46.5±28.29
† Mann Whitney U test, Data are median (min-max). ‡ Student's t-test, Data are mean±SD. WBC: White blood cell, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein.			

Table 4. Echocardiographic features, microbiologic etiology, and outcome of patients with infective endocarditis				
	Patients who survived (n=46)	Patients who died (n=26)	Total patients (n=72)	p-Value
Left-sided IE	33 (71.7%)	25 (96.2%)	58 (80.6%)	**0.028†**
Valvular involvement				
Aortic	11 (23.9%)	12 (46.2%)	23 (31.9%)	0.093†
Mitral	21 (45.7%)	11 (42.3%)	32 (44.4%)	0.978†
Tricuspid	4 (8.7%)	1 (3.8%)	5 (6.9%)	0.647‡
Two valves	1 (2.2%)	2 (7.7%)	3 (4.2%)	0.294‡
Vegetation size of≥10mm	31 (67.4%)	14 (53.8%)	45 (62.5%)	0.375†
Mobile vegetation	29 (63.0%)	15 (57.7%)	44 (61.1%)	0.845†
Perivalvuler complications	12 (26.1%)	13 (50.0%)	25 (34.7%)	0.074†
Paravalvuler abscess	3 (6.5%)	5 (19.2%)	8 (11.1%)	0.128‡
Perforation	1 (2.2%)	4 (15.4%)	5 (6.9%)	0.054‡
Rupture of the leaflet	5 (10.9%)	7 (26.9%)	12 (16.7%)	0.104‡
Complications	21 (45.7%)	23 (88.5%)	44 (61.1%)	**<0.001†**
Heart failure	5 (10.9%)	17 (65.4%)	22 (30.6%)	**<0.001†**
Renal failure	6 (13.0%)	12 (46.2%)	18 (25.0%)	**0.005†**
Embolic events	17 (37.0%)	18 (69.2%)	35 (48.6%)	**0.017†**
Cranial embolism and/or in-farct	8 (17.4%)	11 (42.3%)	19 (26.4%)	**0.043†**
Lung embolism	5 (10.9%)	7 (26.9%)	12 (16.7%)	0.104‡
Surgery	10 (21.7%)	5 (19.2%)	15 (20.8%)	>0.999†
Microbiology				
Culture negative	15 (32.6%)	9 (34.6%)	24 (33.3%)	>0.999†
Staphylococcus spp.	13 (28.3%)	8 (30.8%)	21 (29.2%)	>0.999†
Streptococcus spp.	9 (19.6%)	3 (11.5%)	12 (16.7%)	0.517‡
Enterococcus spp.	5 (10.9%)	3 (11.5%)	8 (11.1%)	>0.999‡
Other bacteria	4 (8.7%)	3 (11.5%)	7 (9.7%)	0.698‡
† Chi-square test, ‡ Fisher's test. Data are n (%).				

Table 5. Predictors of mortality in patients with infective endocarditis.					
	Odds ratio	%95 CI		Wald	p-Value
Invasive procedure before IE	6.825	1.488	31.317	6.105	**0.013**
Lower platelet levels †	1.117	1.039	1.202	8.866	**0.003**
Heart failure	29.291	5.910	145.159	17.104	**<0.001**
† Effect on mortality for each decrease of 10000 /μL.					

This study evaluated the epidemiological, clinical presentations in patients with definite IE and estimated the outcomes and changes in characteristics of the disease. Invasive procedures, heart failure, and lower platelet levels were found independent predictors for mortality.

The mean age of this cohort was (48.5±17.6 years) younger than developed countries, but older than what was reported in the studies from the 1990s in Turkey and developing countries.[9,10,12-14] Mean age was found closer to the mean age in a multicenter study in Turkey.[11] Worldwide, a study has found an increased age among IE patients.[4] Similar studies conducted in Turkey and around the world have demonstrated that males comprise the vast majority of endocarditis cases; this pattern was also observed in the present study.[4,15,16] Although chronic rheumatic heart disease has been seen in decreasing rates, it is still a significant etiological manifestation in our country.[17] In Turkey, HIV positivity has been increasing but there was no HIV positive patient and in our cohort.[18] Some studies conducted in the United States have reported an increased IE incidence related to IVDU, but we had only two iv drug users.[19,20]

Blood culture positivity which one of the major criteria in the diagnosis, was low in this study similar to the studies in Turkey.[21,22] BCNE (blood culture negative endocarditis) occurs more frequently in developing countries and poses a therapeutic challenge.[7,23,24] Difficulties to identify the causative microorganism of IE with traditional methods are associated with high BCNE rates. Molecular and serological methods are necessary to identify microorganisms.[25] There were no fastidious bacteria such as the HACEK group in this study because blood cultures and molecular methods were not processed routinely for identification of these. A review has shown that BCNE percentage decreased during the last decade because of improved laboratory techniques and culture methods.[4] In this study, the BCNE percentage was lower in the period 2014-2017 (27.3%), but this was not statistically significant. As 59.7% of our patients had previous use of antibiotics, we believe this was an important reason for our high number of BCNE (33.3%). Lamas et al. reported that the BCNE rate was 40% and antibiotic use before blood culture collection was 74%.[7]

Staphylococcus aureus was the most frequent causative microorganism in our cohort. A systematic review showed that S. aureus was the most common agent of IE etiology in the world, except for the Asia continent.[6] A systematic review conducted by Slipczuk et al. demonstrated that staphylococcal and enterococcal IE percentages increased worldwide in the last decade.[4] In this study, all enterococcal cases (n=8) were seen in years between 2014-2017. Brucellosis is an endemic zoonotic disease in Turkey. Endocarditis may be a more common complication of systemic brucellosis in countries where there is a high prevalence of brucellosis and rheumatic heart disease.[26] Surprisingly, in a study that evaluated complications of 700 brucellosis cases, IE was not mentioned.[27] Brucella endocarditis was detected in very few patients in some studies which have a small sample size like this study in Turkey.[22,28] But when the study sample size becomes larger, Brucella endocarditis cases are increased.[17]

Antimicrobial resistance was not a major problem in this study. Only three streptococcus isolates were resistant to penicillin. In a previous study, all streptococcus strains

(n=63) isolated from endocarditis cases were sensitive to penicillin.[17] The methicillin resistance rate among S. aureus strains (28.6%) is similar to Turkey in general (23%).[29] We observed that β- lactams were the most frequently used antimicrobial drugs in our study which is compatible with the resistance profile of microorganisms and current treatment guidelines.[2]

Surgery is crucial for optimal treatment in complicated IE.[30] In this study, despite the planning of surgery in many patients, a minority of the patients were able to undergo surgery for the reason of rejection or contraindication. Surgical treatment has been reported as a protective factor for mortality in recent studies.[16,17] We did not find any difference in the surgical intervention rate between the fatal and nonfatal groups. In our study, 26.4% of the patients died in hospital, whereas similar studies published in Turkey reported mortality rates of 28.6–33%.[11,17,21] The mortality rate in our study appears to be generally high and there was no significant difference in mortality between the consecutive periods (39.3%, 34.1% respectively).

In this study, older age was associated with mortality. Korem et al. found that age is the only predictor of mortality in multivariate analysis. In their study health care source of infection, CNS events, and new renal failure were associated with mortality like our study. According to our results, the presence of the comorbid condition, left-sided endocarditis, heart failure, embolic event, lower platelet level, higher urea, creatinine, and bilirubin levels were the other parameters associated with poor prognosis of IE. When looking at the laboratory findings; higher C-reactive protein (CRP), white blood cell count, creatinine, and lower albumin levels were associated with mortality in previous studies.[13,31,32]

Heart failure, the invasive procedure before IE, and lower platelet levels were independently associated with mortality. The largest study from Turkey has demonstrated that higher platelet and hemoglobin levels were protective factors against mortality.[17] Numerous studies have shown that heart failure was an independent risk factor of mortality.[11,13,14] Delahaye et.al. reported that septic shock, cerebral hemorrhage, left-sided IE, lower Glasgow coma scale score, higher CRP levels, history of immunosuppression, history of heart failure, and insulin-requiring diabetes mellitus were independent predictors of mortality.[13] Another study from China has shown that age≥60 years, heart failure, diabetes, and the presence of Staphylococcus aureus or gram-negative bacilli were the major risk factors related to death.[14] It was reported half of the patients (52%) develop heart failure in the Indian cohort.[33] In this cohort, there is no relationship between causative agents and mortality. It can be explained by our small sample size and high rate of culture negativity. Sıegman-Igra et al. reported that hospital-acquired and healthcare-associated IE cases had more invasive procedures (79%) than community-acquired IE cases (69%).[34] It suggests that the importance of health-care acquisition before IE, like this study.

Because increases in the elderly population, increases in chronic illness, and increases in exposure to health care procedures; including dental procedures, intracardiac and vascular devices, hemodialysis, may increase the incidence of endocarditis and disease-related mortality.[1,2,4] The two periods analysis in this study showed an increase in the invasive procedures before IE and an increasing number of enterococcal cases; on the contrary no improvement in survival. A study from Italy showed an increased healthcare exposure similar to this study.[1]

In conclusion, IE patients' age is becoming greater in Turkey. Culture-negative IE remains a problem in our country. Invasive procedures before IE was related to mortality. It highlights the importance of non-specific infection control measures in hospitals. The extensive use of invasive procedures can change the spectrum of microorganisms of IE etiology. Because of such changes in IE, prophylaxis, and treatment regimens should be investigated in new studies. Complications such as heart failure or CNS events

are common and lead to higher mortality, so IE cases must be monitored closely and multidisciplinary. IE presents nonspecific symptoms and clinical findings. Because of increased health-related procedures, the diagnosis should be kept in mind in patients who have risk factors or not. Knowledge of local epidemiology and prevalence of IE is required.

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Limitations of the study

This is an observational study of a small group from one center. But our hospital is a tertiary referral center that accepts patients from many parts of Turkey. The study population was collected using ICD-10-CM codes. All patients with endocarditis may not be assessed due to diagnostic deficiencies in the hospital system resulting from user coding mistakes. Because of the retrospective design, some clinical information was limited in patients' files. Microbiological tests other than culture (Coxiella, Bartonella testing… etc.) were applied to very few patients.

Authors' contributions

SK conceived the idea of the study and coordinated the data collection. SK and EA analyzed the data and drafted the manuscript. EA and HB helped in drafting and revising the manuscript. BO, AB, AA participated in data collection and analysis. All authors have read and approved the final manuscript.

The authors declare no conflicts of interest.

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The data that support the findings of this study are available from the corresponding author, [SK], upon request.

Ethical Approval

Ethics committee approval was obtained for this study from Ankara Numune Training and Research Hospital (confirmation date and number: 29.03.2017, 1320/2017). This study was conducted by the principles of the Declaration of Helsinki.

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