Profile of infective endocarditis cases at a tertiary hospital in Turkey: our 15-year experience

Türkiye'de üçüncü basamak bir hastanede enfektif endokardit olgularının profili: 15 yıllık deneyimimiz

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ABSTRACT

Background: This study aims to evaluate the clinical, echocardiographic, and microbiological profile and in-hospital complication and mortality rates of infective endocarditis cases in the tertiary setting.

Methods: A total of 210 consecutive cases (138 males, 72 females; mean age 48.8±17.9 years; range, 18 to 89 years) who were diagnosed with definite infective endocarditis based on the modified Duke criteria and treated between September 2000 and September 2015 were retrospectively analyzed.

Results: The rate of prosthetic valve infective endocarditis was 12.3%. Rheumatic heart disease was the most common predisposing factor (20.5%). Transthoracic and/or transesophageal echocardiography showed a vegetation in 174 cases (82.9%). Causative microorganisms were identified in 119 cases (56.7%) as *Staphylococci* (30.5%), *Streptococci* (15.2%), and *Enterococci* (7.6%). Cultures were negative in 91 cases (43.3%). Surgical therapy was necessary in 111 cases (53%). Twenty-four percent of cases had a total recovery with appropriate antibiotherapy without needing any surgical procedures. The most common complications were septic embolism (25.2%) and congestive heart failure (13.4%). In-hospital mortality occurred in 41 cases (19.5%).

Conclusion: Our study results show that infective endocarditis is still associated with high in-hospital mortality and morbidity rates.

Keywords: Blood culture; epidemiology; infective endocarditis; rheumatic heart disease; vegetation.

ÖZ

Amaç: Bu çalışmada üçüncü basamak sağlık hizmetinde enfektif endokardit olgularının klinik, ekokardiyografik ve mikrobiyolojik profili ve hastane komplikasyon ve mortalite oranları değerlendirildi.

Çalışma planı: Eylül 2000 - Eylül 2015 tarihleri arasında modifiye Duke kriterlerine göre kesin enfektif endokardit tanısı konan ve tedavi edilen ardışık 210 olgu (138 erkek, 72 kadın; ort. yaş 48.8±17.9 yıl; dağılım 18-89 yıl) retrospektif olarak incelendi.

Bulgular: Protez kapak enfektif endokardit oranı %12.3 idi. En sık görülen yatkınlaştırıcı faktör, romatizmal kalp hastalığı (%20.5) idi. Yüz yetmiş dört olguda (%82.9) transtorasik veya transözofageal ekokardiyografi ile vejetasyon saptandı. Etken mikroorganizmalar *Stafilokoklar* (%30.5), *Streptokoklar* (%15.2) ve *Enterokoklar* (%7.6) olmak üzere 119 olguda izole edildi (%56.7). Doksan bir olgunun (%43.3) kültürü negatifti. Cerrahi tedavi 111 olguya (%53) gerekli oldu. Olguların %24'ünde uygun antibiyotik tedavisi ile cerrahi işleme gereksinim olmaksızın tam iyileşme sağlandı. En sık gözlenen komplikasyonlar septik emboli (%25.2) ve konjestif kalp yetmezliği (%13.4) idi. Kırk bir olguda (%19.5) hastane mortalitesi izlendi.

Sonuç: Çalışma bulgularımız, enfektif endokarditin halen yüksek hastane mortalite ve morbidite oranları ile ilişkili olduğunu göstermektedir.

Anahtar sözcükler: Kan kültürü; epidemiyoloji; enfektif endokardit; romatizmal kalp hastalığı; vejetasyon.

Infective endocarditis (IE) is defined as an infection of the endocardium or heart valves caused by bacteria, fungi or viruses.[1] Despite significant advances in the diagnostic and therapeutic procedures, it is still associated with poor prognosis and high mortality rates.[2] Epidemiological characteristics of IE have remarkably changed in the recent years, particularly in the industrialized countries.[3] In the industrialized countries, IE predominantly affects the individuals without a known valvular disease or elderly with a prosthetic valve.[4,5] As interventional therapeutic procedures become available with the improvements in healthcare, *Staphylococci* stand out as the most common cause of IE.[3] However, acute rheumatic fever and subsequent rheumatic heart disease (RHD) still remain to be the most significant risk factors in the developing countries, where affected patients are mostly the young individuals and *Streptococci* are the most commonly isolated infectious microorganisms.[6]

In this study, we aimed to evaluate the clinical, echocardiographic, and microbiological profile and in-hospital complication and mortality rates of IE cases in the tertiary setting.

PATIENTS AND METHODS

This retrospective, single-center study included a total of 210 consecutive patients (138 males, 72 females; mean age: 48.8±17.9 years; range 18 to 89 years) who were diagnosed with definite IE based on the modified Duke criteria[7,8] and treated between September 2000 and September 2015. Patients diagnosed with 'possible IE' based on the diagnostic criteria were excluded from the study. Medical records of all included patients were reviewed and missing and unclear data records were excluded. The study protocol was approved by local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data assessment

Data available in the medical records of the patients were analyzed and the following information were recorded on patient-specific clinical case report forms: age, gender, history of cardiac disorders or cardiac surgeries, comorbidities, cardiac and non-cardiac risk factors, predisposing conditions and interventions for IE, clinical signs and symptoms of IE, physical examination findings, laboratory and imaging assessments, transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TEE) data, microbiological profiles, cardiac and extra-cardiac complications of IE, medical and surgical treatment regimens, early outcomes of IE and in-hospital mortality data.

Laboratory tests and imaging assessments

Patients with three independent blood culture samples obtained during hospitalization, complete blood count analyzed from peripheral venous blood samples, total urine analysis performed and abdominal ultrasonographic examination were included into the study. Anemia was defined as a hemoglobin level of <13 mg/dL for men or <12 mg/dL for women,[9] leukocytosis as a white blood cell count of >12,000/mm,[3] and thrombocytopenia as a platelet count of <15,0000/mm³. Hepatomegaly or splenomegaly were detected by abdominal ultrasonography.[10]

Echocardiographic examination

Transthoracic echocardiography was performed in all patients during hospitalization and periodically after discharge. Transesophageal echocardiography was performed, when necessary.

Statistical analysis

Data were expressed as mean ± standard deviation and analyzed statistically using the Student's t-test for continuous variables and the chi-square test for discrete variables.

RESULTS

Demographical and clinical data

Table 1 shows the demographical, clinical, and laboratory data of 210 patients diagnosed with IE. The male-to-female ratio was 1.91. Totally, 113 patients (53.8%) referred to the hospital and received IE diagnosis within the first 30 days after the symptom onset. The time from symptom onset to hospital referral and diagnosis was 31 to 90 days in 77 (36.7%) and longer than 90 days in 20 patients (9.5%). The most common symptoms at presentation were fever (≥38 °C) (n=182, 86.7%), fatigue (n=151, 71.9%), dyspnea (n=88, 41.9%), weight loss (n=84, 40%), and muscle-joint pains (n=34, 16.2%). Cardiac murmur was the most common physical examination finding in 185 patients (88.1%) with Grade 2/6 or higher cardiac murmur. Other frequent physical examination findings were rales or reduced/absent breath sounds on lung auscultation (46.2%), hepatomegaly (34.8%), and splenomegaly (31.9%) confirmed by abdominal ultrasonography and vascular or immunological phenomena (21%).

Risk factors and predisposing heart diseases

The most common predisposing risk factor was RHD reported in 43 patients (20.5%). The most frequent cardiac risk factors following RHD were history of

Table 1. Demographic, clinical and laboratory data of patients diagnosed with infective endocarditis (n=210)

	n	%	Mean±SD	Ratio
Demographic characteristics				
Male/female				1.91
Age (years)			48.8±17.9	
Gender				
Males	138	66	50±12	
Females	72	44	45±18	
Symptoms				
Fever	182	86.7		
Fatigue	151	71.9		
Dyspnea	88	41.9		
Weight loss	84	40		
Muscle and joint pains	34	16.2		
Physical examination findings				
Cardiac murmur	185	88.1		
Lung auscultation findings	97	46.2		
Hepatomegaly	3	34.8		
Splenomegaly	67	31.9		
Peripheral infective endocarditis signs	44	20.9		
Laboratory data				
Anemia	183	87.1		
Leucocytosis	138	65.7		
Thrombocytopenia	63	30		
Hematuria/proteinuria	83	39.5		

SD: Standard deviation.

prosthetic (mechanical or biological) valve operation or surgical valve repair (15.3%), and congenital heart diseases (6.7%). Other cardiac risk factors included the presence/implantation of a pacemaker, degenerative valvular diseases, and previous history of IE. The most common non-cardiac risk factors and predisposing conditions included the history of dental interventions (8.1%), central or peripheral venous catheterization (6.7%), chronic renal failure (5.2%), recent (within the previous month) history of colonoscopy (2.9%), and immunosuppressive therapy (2.9%). Any risk factor or predisposing condition was not found in 134 patients (63.8%) (Table 2).

Echocardiographic data

All patients underwent TTE during hospitalization and periodically after discharge (n=210, 100%). Additionally, TEE was performed in patients with poor echogenicity or insufficient imaging on TTE, equivocal clinical diagnosis, suspected complications and in patients under high-risk of developing complications (n=145, 69%). Combination of the two imaging modalities demonstrated the presence of vegetation in 174 patients (82.9%), while no vegetation was observed in 36 (17.1%) patients. The majority of patients presented with left-sided IE and right-sided IE was relatively rare. Mitral or aortic valve endocarditis was reported in 192 patients (91.4%). Of the remaining patients, 11 patients (5.2%) had tricuspid valve endocarditis, four (2%) had pacemaker lead endocarditis, and only one patient had pulmonary valve endocarditis. In terms of the valve structures, the infected valve was a native valve in 181 patients (86.2%) and a prosthetic valve (mechanical or biological) in 26 patients (12.3%). The most frequently affected native valve was the mitral valve (n=80, 38.1%), while aortic valve (n=13, 6.2%) was the most frequently involved prosthetic valve (Table 3).

Microbiological characteristics

Table 4 shows the frequency and distribution of the infectious microorganisms. Blood culture samples were obtained from all patients, and 119 patients (56.7%) had positive blood culture results. The most frequently isolated infectious agents were *Staphylococci* (n=64, 30.5%), followed

Table 2. Underlying heart diseases, risk factors and predisposing conditions in patients with infective endocarditis (n=210)

	n	%
Patients without any heart disease or risk factor	134	63.8
Cardiac risk factors		
Rheumatic heart disease	43	20.5
Prosthetic heart valve or surgical valve repair	32	15.3
Presence or implantation of a pacemaker	15	7.2
Congenital heart diseases	14	6.7
Ventricular septal defect	4	1.9
Bicuspid aortic valve	4	1.9
Mitral valve prolapse	2	1
Hypertrophic cardiomyopathy	2	1
Patent ductus arteriosus	1	0.5
Tetralogy of Fallot	1	0.5
Degenerative valvular disease	4	1.9
History of infective endocarditis	2	1
Non-cardiac risk factors		
Dental intervention	17	8.1
Central and/or peripheral venous catheterization	14	6.7
Chronic renal failure	11	5.2
Colonoscopy (within the previous 30 days)	6	2.9
Immunosuppressive therapy	6	2.9

by *Streptococci* (n=32, 15.2%), *Enterococci* (n=16, 7.6%), and other microorganisms (Gram- and fungi) (n=7, 3.4%). No infectious agent was isolated in the blood cultures of 91 patients (43.3%).

Complications

Infective endocarditis related in-hospital complications who developed during the treatment and follow-up periods were analyzed in two groups as cranial (neurological) and extra-cranial complications. Cranial complications developed in 47 patients (22.3%). The most common cranial complication was cerebral septic embolism and subsequent cerebral infarctions, followed in order of frequency by intracranial hemorrhage, meningitis/encephalitis, cerebral abscess and transient ischemic attack. Extra-cranial complications developed in 51.9% of the patients, the most frequently reported complications being septic embolisms (n=53, 25.2%) and congestive heart failure resulting in the New York Heart Association (NYHA) Class III-IV heart failure symptoms (n=28, 13.4%). To a lesser extent, acute renal failure, spleen abscess, empyema, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), aortic root abscess and subsequent full AV block were also reported in this patient group. Distribution and frequencies of the

Table 3. Echocardiographic data

	n	%
Type of affected valve		
Prosthetic valve endocarditis*	26	12.3
Involved cardiac region and affected valve		
Left-sided infective endocarditis	192	91.4
Right-sided infective endocarditis	16	7.6
Two-sided infective endocarditis†	2	1
Presence of vegetation‡		
Vegetation detected	174	82.9
Vegetation not detected	36	17.1

* Mechanical or biological prosthetic valve; † One patient had mitral, aortic and tricuspid involvement, one patient had mitral-tricuspid involvement; ‡ Detected by combined use of transthoracic and transesophageal echocardiography.

Table 4. Microbiological profile

	n	%
Microbial growth in culture medium	**119**	**56.7**
Staphylococci	**64**	**30.5**
Methicillin sensitive *Staphylococcus aureus*	23	11
Methicillin resistant *Staphylococcus aureus*	22	10.5
Staphylococcus epidermidis and other CNS	19	9
Streptococci	**32**	**15.2**
Streptococcus viridans	26	12.4
Other streptococci	6	2.8
Enterococci	**16**	**7.6**
Other microorganisms	**7**	**3.4**
No microbial growth in culture medium	**91**	**43.3**

CNS: Coagulase-negative *Staphylococcus.*

cranial and extra-cranial complications are shown in Table 5.

Treatment and prognosis

While 24.3% of the patients were cured by appropriate antibiotherapy without requiring a surgical intervention, 111 (53%) underwent surgery for valve replacement or valve repair. The rate of in-hospital mortality was 19.5% (n=41).

DISCUSSION

Findings of the present study revealed the changing etiological characteristics of IE patients at a tertiary hospital in Turkey. In addition, this study demonstrated the clinical outcomes, risk factors, microbiological, and echocardiographic data, complications during the course of the disease, and in-hospital mortality rates associated with IE.

Despite all improvements in diagnostic imaging modalities, antibiotherapy regimens and surgical methods, IE is still associated with high rates of mortality and morbiditl.[2] As shown in clinical trials, IE incidence has been growing in the recent years, and epidemiological features of the disease have considerably changed.[5]

The mean age of IE patients at disease onset significantly varies between studies, ranges from 36 to 69 years.[4] This difference mainly originates from the Western populations, where IE is a disease of the elderly. On the other hand, the disease manifests itself at earlier ages in the underdeveloped and developing countries, where RHD still remains to be a frequent entity.[2] According to data collected in the Euro Heart Survey study, the mean age of patients at IE onset was 56±17 years in Europe, while a study performed in

Table 5. Cranial and extra-cranial complications of infective endocarditis

	n	%
Cranial complications	47	22.3
Cerebral septic embolism and cerebral infarction	34	16.2
Intracranial hemorrhage	6	2.9
Meningitis/encephalitis	3	1.4
Cerebral abscess	2	1
Transient ischemic attack	2	1
Extra-cranial complications	109	51.9
Septic embolism*	53	25.2
Congestive heart failure‡	28	13.4
Acute renal failure	10	4.8
Spleen abscess	7	3.3
Acute respiratory distress syndrome	3	1.4
Disseminated intravascular coagulation	3	1.4

* Systemic embolisms other than cerebral embolism; ‡ Patients with NYHA Class III-IV symptoms and/or clinical picture of acute pulmonary edema.

Greece, one of Turkey's neighbor countries, reported a mean age of 54±17 years.[11,12] The mean age of patients at IE onset is as low as 32 years in countries such as Tunisia and India.[13,14] Studies performed in Turkey in different time points reported the mean age at disease onset varying between 45 and 47 years.[15-17]

Furthermore, IE develops more frequently in men; however, the reason underlying higher proportion of men is poorly understood, and the Guidelines on the prevention, diagnosis, and treatment of IE published by the European Society of Cardiology estimates a male-to-female ratio of 2:1.[2] Similarly, in the present study, we found a male-to-female ratio of 1.91.

Although IE patients included in the present study manifested with a wide range of signs and symptoms, in consistent with the previous studies,[7,8,11-18] the most common symptom was fever (86.7%), while the most common physical examination finding was murmur (88.1%). The patients who received the diagnosis of IE within the first 30 days following symptom onset accounted only for 53.8% of the study population. The rate of such patients was found to be 77% in the international, multi-central International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS).[8] A detailed assessment of the discharge reports of the remaining patients showed that these patients had several referrals to healthcare providers during the period before diagnosis and were treated with empirical antibiotherapies due to undefinite or incorrect diagnoses. This finding indicates that physicians do not always consider the diagnosis of IE, and the disease is occasionally misdiagnosed. Manifestation of the disease with atypical symptoms such as diuresis, hematuresis, and cough, and inability to perform an optimal echocardiographic examination due to limited echogenicity and, thereby, failure to notice vegetation and inadequate growth of anaerobic and intracellular microorganisms in growth culture media may be listed among the other factors of a delayed diagnosis.

The most common predisposing heart disease in developing countries is RHD, which was reported at rates varying between 28-39% in the studies performed in different countries.[14-16,19] On the other hand, the most common predisposing condition observed in the developed western societies is degenerative valvular diseases, which is in line with the aging population.[5,8] In the present study, although the most common predisposing risk factor was RHD, the rate of RHD was found to be lower than the rates previously reported by other Turkish studies.[15,16] History of prosthetic (mechanical or biological) valve operation

or surgical valve repair and dental interventions were found to be the other significant predisposing risk factors. In the multi-central, prospective 'The Endocarditis Infecciosa en la RepublicaArgentina-2 Study (EIRA-2)', 15.9% of IE cases had prosthetic valves, while this rate was 15.3% in the present study.[7]

Echocardiography is the most widely used diagnostic test for the diagnosis and monitoring of IE. In the present study, all patients underwent TTE. Current guidelines recommend TEE to be performed in cases with normal TTE findings, despite a high clinical suspicion of IE, in cases where TTE images are suboptimal, and for the purposes of measuring the extent of vegetation and diagnosing complications such as abscess and dehiscence.[2] In previous Turkish studies, TEE was performed in 37 to 56% of the cases.[16,17,20] This rate varies between 59% and 65% in the international, multi-central studies.[7,8] In the present study, 69% of the patients underwent TEE, a rate which is considerably higher than the rates reported by previous studies conducted in Turkey.[16,17,20] When these two modalities were combined, vegetation was identified in 87.1% of the patients in the ICE-PCS trial, and similarly, demonstrated vegetation in 82.9% of our cases. As shown in Table 3, left-sided IE was more common than right-sided IE in our patient population, a finding which is in consistent with the EIRA-2 study showing right-sided endocarditis in 11% of the cases.[7] On the contrary, in their prospective study performed in Europe, Hill et al.[5] reported right-sided endocarditis in 18% of their cases. The lower rate of right-sided endocarditis in our series, compared to the previously reported rates in THE European populations, can be due to less frequent implementation of invasive healthcare procedures, such as hemodialysis and pacemaking, relatively small sample size in the study population who underwent tricuspid valve surgery, and absence of intravenous-drug dependent patients.

Furthermore, in Western countries, increase in the rate of elderly population and subsequent rise in the frequency of degenerative valvular diseases, widespread implementation of invasive healthcare procedures and prosthetic valve operations, and the increase in intravenous drug usage have resulted in a change in the epidemiological characteristics of IE in the past decades.[2] In these societies, contrary to the past, *Staphylococcus spp.* stand out as the most frequently isolated IE agents, while the frequency of *Streptococcus* infections declines gradually.[2,4,21,22] In contrast, RHD is still a frequent entity in underdeveloped and developing countries and, therefore, IE manifests

itself at younger ages and *Streptococci* remain to be the most frequently isolated IE agent.[2,7,12,21] The most frequently isolated microorganism in the previous studies performed in Turkey was *Staphylococcus aureus*; however, its incidence considerably varied between studies.[15,17,20] In a multi-central IE study performed by Elbey et al.,[16] the rate of *Staphylococcus* infection was reported as 29%. Similarly, the most frequently isolated IE agent in the present study was *Staphylococcus* (30.5%). We obtained blood and urine samples for growth culture analyses from all IE patients during hospitalization, before the initiation of antibiotherapy; however, an infectious microorganism was not isolated in 43.3% of the cases. This rate is considerably higher than the rates reported in the Western patient series. The ratio of negative blood culture growth was reported as 11% in the study of Hill et al.,[5] 10.8% in EIRA-2 study, and 10% in ICE-PCS study.[7,8] This rate varied between 35 and 43% in previous Turkish studies, reaching up to 59% in studies performed in underdeveloped societies.[14,15,16,20] The most important causes underlying such a high rate of negative culture growth include empirical use of multiple antibiotic therapies before the diagnosis, inappropriate sampling and/or growth medium to cultivate anaerobic and fungal microorganisms, and failure to grow intracellular microorganisms by traditional growth culture methods[2] The most common predisposing factor in the present study was RHD, while prosthetic valve endocarditis was reported only in 12.3% of the patients. Despite RHD was common and prosthetic valve endocarditis was observed to a lesser extent in the present study, it is a remarkable finding and worthy to discuss that the most frequently isolated infectious microorganism was *Staphylococcus*, while *Streptococcus* was detected only in 15.2% of the patients. As previously indicated, an infectious microorganism was unable to be isolated in 43.3% of the patients diagnosed with IE. It is also known that 46.2% of the patients received late IE diagnosis (30 or more days after symptom onset) and used multiple empirical antibiotherapies during this period. The low rate of *Streptococcus* isolation despite high frequency of RHD can be attributed to the antibiotics used before the IE diagnosis and susceptibility of the microorganisms to the given treatment regimens.

In addition, congestive heart failure is the most frequent complication which develops during clinical follow-up of patients with IE.[15,16] The rate of heart failure development during IE course, as reported by previous studies, varied between 31% and 53%.[14,15,16,20] In the study of Leblebicioglu et al.,[17] the most frequent

complications were embolic events (33%). In the present study, we assessed in-hospital complications in two groups as cranial (22.3%) and extra-cranial (51.9%) complications. The most common cranial complications were ischemic cerebrovascular events developing on the basis of septic embolization. Contrary to the literature, the most frequent extra-cranial complication was systemic embolism (25.2%). On the other hand, heart failure developed in 13.4% of the patients, which is inconsistent with the previous reports.[15,16] This remarkable discrepancy may be due to the differences between the definitions of "heart failure" used in each study. In the present study, cases of heart failure developing on the basis of IE were defined as those accompanied by NYHA Class III-IV symptoms or clinical presentation of acute lung edema. We did not include the patients with subclinical or mild heart failure symptoms to this group. Another point to take into consideration is that the rate of surgical treatment was relatively low in the studies that reported high rates of heart failure.[14,15] As aforementioned, the rate of heart failure varied between 31% and 53% in the literature, while the rate of surgical treatment ranged between 15% and 27%.[7,14,15] In the present study, 24.3% of the patients were cured by antibiotherapy alone, while 53% underwent a surgical intervention in combination with antibiotherapy. Emergency surgery was performed within the first 24 hours of worsening of the clinical condition in patients with pulmonary edema in whom severe aortic, and mitral insufficiency developed and early surgery (<7 days) was decided for patients in whom local spread of infection was seen, as in perivalvular abscess formation, false aneurysm or fistula development. In addition, surgery was performed due to the cranial or systemic septic embolism and also high-risk of embolism due to motile vegetation >1 cm located on the left side identified on echocardiographic examination. Elective surgery was performed to control infection in patients in whom, apart from these indications, persistent fever or blood culture positivity lasting for more than 7 to 10 days, despite appropriate antibiotic therapy. We believe that surgical interventions, when performed for the right indication and at the proper time, can reduce the rate of heart failure and septic embolism which may potentially develop during disease course.

Despite recent improvements in antibiotherapy regimens and surgical interventions, IE is still associated with high rates of mortality and morbidity. The rates reported by previous studies varied between 14% and 29%.[7,8,23,24] In addition, mortality rates reported during the course of IE in Turkish patient series ranged between 15% and 33%.[15,16,25,26] The rate

of in-hospital mortality was found to be 19.5% in the present study.

Nonetheless, there are some limitations to this study. First, it has a retrospective design. Second, it is a single-center study in the tertiary setting. Therefore, the majority of the patients were referred from first- and second-line healthcare centers, and they were high-risk patients with multiple risk factors and comorbidities. These factors might have resulted in an untoward bias in patient selection and heterogeneity of the patient population. Third, the use of antibiotics in this patient group before their admission to our hospital might have masked the signs and symptoms at presentation and, more importantly, hindered the cultivation of infectious agents in growth cultures. All these factors might have led to false interpretations of the study results. It is, therefore, recommended to consider the above limitations before generalizing our findings for the overall population.

In conclusion, epidemiological characteristics of infective endocarditis have changed tremendously in Turkey, as in the whole world. In Turkey, IE patients present with this disease at younger ages, compared to the Western populations, and at older ages, compared to underdeveloped countries. Although the frequency of rheumatic heart disease has been reducing, it still remains to be the most common predisposing factor. In consistent with the studies conducted in the developed Western countries, our findings also show that the most common infectious agent is *Staphylococcus*. Furthermore, despite all improvements in diagnostic and therapeutic procedures, infective endocarditis still remains to be associated with high in-hospital mortality and morbidity rates.

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