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Original Article

Evaluation of epidemiological and microbiological characteristics, clinical features, and outcomes of adult patients with infective endocarditis in Mashhad, Iran

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Abstract

Introduction: Infective endocarditis (IE) is a serious problem with high morbidity and mortality. However, there is a paucity of data regarding its epidemiology in non-high-income settings. Here, we described the characteristics of patients with IE.
Methodology: Between March 2012 to March 2020, all adults (≥ 16 years) with a diagnosis of IE who were admitted to a university hospital in Mashhad, Iran, were included in the study.
Results: We evaluated 46 cases of IE with a median age of 42 years (interquartile range 31 to 58.3 years), of whom 21 (46%) had a definite diagnosis. The presence of a prosthetic valve or intracardiac device was the leading predisposing factor (N = 14, 30%). The etiology of IE in 22 subjects (48%) remained unknown. *Staphylococcus aureus* (N = 12, 26%) was the most common causative pathogen. Echocardiography revealed the mitral valve as the most affected valve (N = 18, 39%). Intravenous drug users (IVDU) had a higher chance of right-sided IE, as compared to no IVDU patients (odds ratio: 35, 95% CI: 3.7 to 425.0). The most prevalent complications were lung infarction, acute heart failure, and neurologic involvement (N = 5, 11% for each), and 15 patients (33%) died because of IE.
Conclusions: In our study, the median age of IE onset was relatively low. The most frequent predisposing factor was a prosthetic valve or intracardiac device. The proportion of negative blood cultures was unacceptably high. Thus, our findings emphasize promoting laboratory infrastructure, developing a national protocol for early initiation of appropriate treatment, and eliminating predisposing factors.

Key words: Infective endocarditis; epidemiology; microbiology; outcome.

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Introduction

Infective endocarditis (IE) is the infection of the endocardium that affects a small number of people but has high morbidity and mortality [1]. During the past three decades, the incidence of IE and its mortality rate have been steadily rising, particularly in areas with a higher socio-demographic Index (SDI). In 2019, it was anticipated that there were 1,090,527 incident cases of IE worldwide, which resulted in 66,322 fatalities and 1,723,594 disability-adjusted life years [2]. Despite advancements in medical and surgical treatment, IE remains a fatal condition with significant mortality rates, which range from 14 to 22 percent in-hospital and reach 51 percent after ten years [3]. Moreover, the population at risk of IE has increased during previous decades because of several factors, including population aging, the rise in the number of patients receiving hemodialysis for end-stage renal disease, an increase in the usage of cardiac implantable electronic devices, and the increased number of patients with congenital heart disease who survive to adulthood [3–5]. Also, alterations in the disease's microbiology have taken place worldwide, varying among countries [6,7]. Streptococci species, particularly oral cavity flora, have historically been the predominant bacterial pathogens. However, staphylococcal species, including methicillin-resistant strains (MRSA), now represent a substantial growing portion of IE subjects [8].

In high-income countries, the epidemiologic factors that are engaged in the incidence of IE have altered in comparison to the past few decades due to parameters such as an increased life span, a markedly increased number of nosocomial cases, and an increased number of cases of degenerative valvular disease [9,10]. However, a paucity of data is available in developing countries such as Iran [11–13]. In this regard, we aimed to conduct a retrospective study to determine the demographical, microbiological, clinical features, and

outcomes of patients admitted to a referral hospital in Mashhad, Iran, with a diagnosis of IE between March 2012 to March 2020.

Methodology

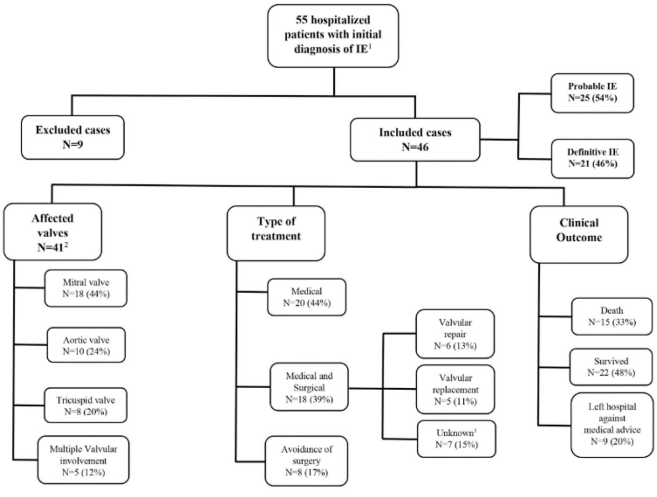
This investigation was a cross-sectional study conducted in the Department of Infectious Diseases between March 2012 to March 2020 on all adults (age 16 or older) with the diagnosis of IE who were admitted to a referral, 1000-bed tertiary care hospital in Mashhad, Iran. First, using ICD-10 codes, patients with a diagnosis of IE were identified. Then, patients' medical records were reviewed to categorize them into definitive and probable based on the modified Duke criteria [7]. Our exclusion criteria were lack or incomplete data regarding the diagnosis of IE (based on the modified Duke criteria), patients younger than 16 years old, and patients with non-infective endocarditis.

Extracted data were gathered using pre-designed checklists. Data comprised demographic features, clinical and laboratory findings, echocardiographic reports, underlying conditions, causative microorganisms (recognized using conventional blood culture and serology), minor and major Duke criteria, and patients' outcomes.

Normality was assessed using Kolmogorov-Smirnov test. Continuous variables were described by median and interquartile range (25th percentile -75th percentile) or mean and standard deviation based on normality. Frequency and percentage were represented as the categorical variables. For univariable analysis, the Mann-Whitney U-test (normally distributed data) and independent t-test (not normally distributed data) were used for continuous variables, while the Fisher exact test or the Chi-square test were used for categorical variables, as appropriate. Additionally, we interpreted the strength of association based on Olivier *et al.* study [14]. All data were analyzed using SPSS software (version 23, SPSS Inc., Chicago, IL, USA).

The Ethics Committee of the Mashhad University of Medical Sciences approved this research (ethics code: IR.MUMS.MEDICAL.REC.1398.592).

Figure 1. Summary of 55 cases with initial diagnosis of Infective Endocarditis



1 IE: infective myocarditis; 2 Forty-two patients had valvular involvement, of whom one patient with single valve involvement had no data regarding the affected valve; 3 Data regarding the type of surgery were not available for seven of the patients.

Results

Between March 2012 to March 2020, a total of 55 patients were included in our study based on primary screening. Nine cases were excluded (two did not fulfill the modified Duke criteria for definite or probable IE, six were younger than 16, and one had an alternative diagnosis) (Figure 1). The rest of the 46 patients included in our study (median age (25th percentile to 75th percentile) = 42 years (31 to 58.3)), of whom 29 were males (63%) (Table 1).

The most common patients' comorbidity and underlying valvular disease were ischemic heart disease (N = 10, 22%) and mitral valve regurgitation (N = 7,

Table 1. Characteristics of the patients with infective endocarditis.

Characteristic	Total, N = 46
Age (years), median (25th percentile to 75th percentile)	42 (31 to 58.3)
Elderly (≥ 60 years, %)	10 (22)
Gender, male (%)	29 (63)
Educational status (%), N = 29	
No former education	5 (17)
Primary education	17 (59)
Diploma	6 (21)
Academic education	1 (4)
Underlying comorbidities (%)	
Ischemic heart disease	10 (22)
Hypertension	9 (20)
Diabetes mellitus	7 (15)
Chronic kidney disease	6 (13)
History of rheumatic heart disease	3 (7)
Obstructive pulmonary disease	2 (4)
History of kidney transplantation	2 (4)
Active cancer	2 (4)
Stroke	2 (4)
HIV/AIDS	1 (2)
History of cardiac valve disease (%)	
Mitral valve regurgitation	7 (15)
Mitral valve prolapse	4 (9)
Bicuspid aortic valve	3 (7)
Calcific aortic stenosis	2 (4)
Mitral stenosis	2 (4)
History of central venous catheter (%)	7 (15)
Previous history of IE (%)	7 (15)

15%), respectively. A previous episode of IE and a history of central venous catheterization were presented each in seven (15%). Thirty-eight cases (83%) had at least one predisposing factor for IE. The presence of a prosthetic valve or intracardiac device was the most common predisposing factor (N = 14, 30%), followed by structural heart disease (N = 13, 28%) and intravenous drug abuse (N = 11, 24%).

The most common chief complaints among the patients with IE were fever (N = 24, 52%), dyspnea, and seizure, each in six (13%). Eighteen patients (39%) had a cardiac murmur. Thirty patients (71%) were systemic inflammatory response syndrome (SIRS) positive, and two (4%) had splenomegaly.

The etiology of IE remained unknown in 22 (48%). In the rest of the cases, methicillin-sensitive *Staphylococcus aureus* (MSSA) (N = 8, 17%) and methicillin-resistant *S. aureus* (MRSA) (N = 4, 9%) were the most common causative pathogens. Based on serology tests (Wright and 2- mercaptoethanol) brucella species caused IE in two cases.

According to Duke criteria, 21 patients (46%) had a definitive diagnosis of IE. Twelve patients (26%) were blood culture positive based on the criteria, and two (4%) had a biopsy consistent with IE.

Echocardiographic findings showed that 41 patients (89%) had intracardiac vegetation, two (4%) had new partial dehiscence of the prosthetic valve, and one (2%) had new valvular insufficiency. Most of the cases (N = 37, 80%) had single valve involvement, five (11%) had multiple valve involvement, and two (9%) had vegetation on the other parts of the heart (vegetation on the intracardiac device and right atrial wall each in one).

Mitral and aortic were the most commonly affected valves (N = 18, 39%, and N = 10, 22%, respectively), followed by the tricuspid valve (N = 8, 17%), simultaneous involvement of mitral and aortic valves (N = 4, 9%), and simultaneous involvement of aortic, pulmonary, and tricuspid valve (N = 1, 2%). Intravenous drug use (IVDU) was associated with a higher chance of right-sided IE, as compared to no IVDU patients (77.8% vs. 9.1%, $p < 0.001$, odds ratio: 35, 95% confidence interval: 3.7 to 425.0). There was no statistically significant association between the IVDU patients and *S. aureus* (80% vs. 50%, $p = 0.24$, OR: 4, 95% confidence interval: 0.28 to 221.13).

The frequency of minor Duke criteria was as follows: fever (N = 40, 87%), vascular symptoms (N=14, 30%), evidence of minor culture (N = 9, 20%), and immunological symptoms (N = 6, 13%).

Of 46 patients with IE, 25 (54%) experienced complications (Table 2). The most frequent

Table 1 (continued). Characteristics of the patients with infective endocarditis.

Characteristic	Total, N = 46
Chief complaint (%)	
Fever	24 (52)
Dyspnea	6 (13)
Seizure	6 (13)
Loss of consciousness	3 (7)
Knee joint pain	2 (4)
Weakness and lethargy	2 (4)
Pelvic pain	2 (4)
Fever and petechia	1 (2)
Clinical features (%)	
Cardiac murmur	18 (39)
Splenomegaly	2 (4)
Respiratory rate (per minute), N = 38	
< 20	23 (7)
20 to 30	8 (21)
> 30	6 (16)
Intubated	1 (3)
Heart rate (per minute), N = 42	
< 100	22 (52)
More than 100	20 (48)
Laboratory features	
Urine analysis, N = 34	
Leukocyturia[1]	11 (32)
Hematuria[2]	17 (50)
Proteinuria[3]	8 (24)
Complete blood count, N = 41	
Platelet	
Fewer than 150 × 10^9/L	18 (44)
150 to 450 × 10^9/l	22 (54)
More than 450 × 10^9/L	1 (2)
Leukocyte	
Normal	18 (44)
Leukocytosis[4]	23 (56)
Positive systemic inflammatory response syndrome[5], N = 42	30 (71)
Etiology, %	
Unknown	22 (48)
Methicillin-sensitive *Staphylococcus aureus*	8 (17)
Methicillin-resistant *Staphylococcus aureus*	4 (9)
Vancomycin-resistant Enterococcus	3 (7)
Viridans streptococci	2 (4)
Pseudomonas aeruginosa	2 (4)
Brucella species[6]	2 (4)
Escherichia coli	8 (7)
Group B Streptococcus	1 (2)
Candida species	1 (2)
Number of affected valves (%)	
Single	37 (80)
Multiple	5 (11)
No valve involvement	4 (9)
Affected valves, N = 41[7]	
Mitral valve	18 (44)
Aortic valve	10 (24)
Tricuspid valve	8 (20)
Mitral and Aortic valves	4 (10)
Aortic, pulmonary, and tricuspid valves involvement	1 (2)

1 Leukocyte count above 5 per High power field (HPF); 2 Erythrocyte count above 5 per HPF; 3 Based on the dipstick test; 4 Leukocyte count above 11 thousand per microliter; 5 If any two of the following were present: temperature over 38 or under 36 degrees Celsius, a heart rate greater than 90 beats per minute, a respiratory rate greater than 20 breaths per minute, white blood cells more than 12 thousand per microliter or less than 4 thousand per microliter; 6 The diagnosis was made based on serology (Wright and 2-mercaptoethanol); 7 Forty-two patients had valvular involvement, of whom one patient with single valve involvement had no data regarding the affected valve.

complications were lung infarction, acute heart failure, and neurologic involvement (N = 5, 11 for each), followed by acute kidney injury (N = 4, 9%). In addition, in-hospital mortality was 33% (N = 15).

Twenty-six patients (57%) out of 46, required surgical treatment. Of these patients, 18 (39%) underwent surgery in our hospital.

Univariable analysis revealed no significant association between poor outcome (death) and different factors (Table 3).

Discussion

We evaluated 46 cases of IE in an eight-year period with a median age of 42 years (interquartile range 31 to 58.3). Other studies conducted in Iran and its neighboring countries demonstrated a mean age range of 45 to 48.1 [11,15–17]. However, in some cases, the mean age in high-income countries was higher [18–20]. Consistent with previous studies, our results revealed that IE more frequently affected males (N = 29, 63%) than females [18,19,21]. Regarding past investigations in Iran, this rate was about 60% [11,22].

The risk factors of IE are significantly associated with the socio-economic level of countries [6]. For instance, rheumatic heart disease (RHD) is the leading risk factor in low-income countries. On the other hand, in high-income countries, the significant risk factors are prosthetic valves and intracardiac devices [6,7]. Our study showed that the most common predisposing cardiac conditions were the presence of prosthetic valves and intracardiac devices, which were present in nearly one-third of the subjects. However, only three of our patients had a history of RHD, which was lower than those in middle to high-income settings [23–25]. Since numerous patients missed academic education, this might reveal a relationship between the effect of socio-economic level and the incidence of IE. Therefore, designing studies with larger sample sizes and analyzing the possible relationship between the data will help to understand the social risk factors of IE and the prognosis of patients.

IE diagnosis should be considered in patients with compatible clinical features even without a known underlying disease [18,26]. In the current study, about 17% of patients had no former known predisposing factors for IE. Same to our results, prior studies revealed that fever was the main symptom of IE patients [11,18,27]. The prevalence of splenomegaly in our study was much lesser than in another investigation in Iran [22]. The possible reason for the lower number of patients with splenomegaly may be due to patients visiting our center in the early stages of the disease.

Since about half of the patients had negative cultures, the causing pathogen remained anonymous.

Table 2. Complications, treatment, and outcome of patients with infective endocarditis.

	N = 46
Complications[1] (%)	
Lung infarction	5 (11)
Acute heart failure	5 (11)
Neurologic Involvement	5 (11)
Acute kidney injury	4 (9)
Limb ischemia	3 (7)
DIC	2 (4)
Adverse drug reaction	2 (4)
Gastrointestinal bleeding[2]	1 (2)
Septic arthritis	1 (2)
Type of treatment	
Medical	20 (44)
Surgery	18 (39)
Valvular repair	6 (13)
Valvular replacement	5 (11)
Unknown[3]	7 (15)
Failure to perform surgery despite the need for it[4]	8 (17)
Clinical outcome (%)	
Death	15 (33)
Survived	22 (48)
Left hospital against medical advice	9 (20)

1 The complications either occurred during hospitalization or on admission; 2 Due to thrombocytopenia; 3 The data regarding the type of surgery were not available in seven patients; 4 These were due to patient unwillingness and poor candidacy for surgical treatment.

Table 3. Comparing characteristics of survived and dead patients with infective endocarditis.

	Survived[1] (N = 22)	**Death (N = 15)**	***p* value**
Age (years), median (25th percentile to 75th percentile)	39 (30.3 to 44)	43.5 (36 to 72)	0.14
Elderly (≥ 60 years, %)	2 (9)	4 (27)	0.15
Gender, male (%)	17 (77)	10 (67)	0.48
Symptom duration (days), median (25th percentile to 75th percentile)	10 (3 to 20)	12 (3 to 60)	0.52
Diabetes mellitus (%)	2 (9)	2 (13)	0.68
Acute heart failure (%)	2 (9)	4 (27)	0.20
Neurologic involvement (%)	3 (14)	2 (13)	0.98
Staphylococcus aureus etiology (%)	6/10 (60)	4/9 (44)	0.50
Septic emboli (%)	8 (36)	4 (27)	0.54
Need for surgical treatment (%)	11 (50)	8 (53)	0.84

1 Nine patients were excluded from the analysis because they left the hospital before treatment completion.

The frequency of negative culture was considerably higher than in several high-income countries (10-20%) [20,28,29]. This could be due to laboratory errors which may be a consequence of inappropriate laboratory techniques or specimen preparation. In addition, it might be because of antibiotics overuse before obtaining the blood culture. Notably, because our center is a tertiary hospital, several patients had been referred from other centers after antibiotics consumption. Additionally, in some cases, non-bacterial pathogens generate culture-negative IE.

The main pathogen in our study was *S. aureus* which was predominant in studies of high-income countries (26.1%) [6]. The amount of antibiotic consumption, the differences in antibiotic resistance, and the epidemiology of common pathogens in each region would result in variations in microbial profiles [6,8]. The most predominant pathogens of IE are staphylococci and streptococci in high-income and low-income countries, respectively [6,8]. The prevalence of IE caused by staphylococci species has increased in several countries, while the prevalence of streptococcal species infection declined remarkably. The growing trend of staphylococcal endocarditis might be related to the increasing use of intravenous drugs, intravenous catheters, the aging population, and patients on dialysis [6,30,31].

Additionally, the proportion of IE cases caused by MRSA in our study was higher than the regions with low MRSA frequency (with a proportion of 3.7%-7%) [17,21]. Nonetheless, this proportion is lower than in some countries, including the United States (17.5%) and Qatar (11%) [18,32]. However, this comparison should be made with caution due to the high prevalence of negative culture in our study. In this regard, efforts to improve diagnostic tests help determine the microbial profile of each region and design antibiograms for national guidelines. Furthermore, investigation through the microbial profile, especially regions harboring antibiotic resistance, is essential in the case of selecting the proper empirical antibiotic treatment [21,24].

More than 95% of our patients had echocardiographic manifestations. Regarding our limitations in microbiological diagnostic tools, echocardiography is essential for the diagnosis of IE in our center. Due to a lower rate of negative cultures in high-income countries, microbiology tests play a significant role in diagnosing IE [20].

In agreement with other studies [18,24], mitral and aortic were the most commonly affected valves, involving 39% and 22% of patients, respectively. However, other studies highlighted the aortic valve as the most commonly involved valve [22,27,29]. The rate of tricuspid valve involvement among our patients was far higher (N = 8, 20%) than in other studies [18,27,29]. It could be due to a higher frequency of intravenous drug users in this study. Our results revealed that IVDU was related to a higher odd of right-sided IE compared to no IVDU patients (OR: 35, 95% CI: 3.7 to 425), which had a medium to a large effect [14].

In-hospital mortality (N = 11, 24%) was higher compared to previous studies [18,23]. It might be due to some patients' discontent with surgical treatment or delayed diagnosis of IE. Our findings showed no significant relation between mortality and different factors. It could be due to the small sample size of our study, which resulted in low power status. Based on prior studies, aging, *S. aureus* etiology, septic embolism, diabetes mellitus, heart failure, neurologic event, and cardiac abscess were some risk factors associated with a higher risk of mortality [23,24,29,33].

The current study had several limitations. First, the retrospective design of this study and lack of follow-up caused limited information in terms of long-term patients' outcome. Second, the details of medical records were not accessible for all the subjects. Last but not least, regarding the small sample size of our study, the detection of significant associations and drawing conclusions that could be applied to a larger population is difficult.

Conclusions

The present study showed that the median age of IE was relatively low in our center. The primary cardiac predisposing factors were prosthetic valves or intracardiac devices. Furthermore, a considerable proportion of patients were culture negative; among culture-positive cases, *S. aureus* was the predominant identified pathogen. Additionally, a higher frequency of right-sided IE was associated with IVDU. The rate of patients harboring unfavorable outcomes was high, declaring the importance of enhancing laboratory tests, proper and early treatment procedures, and eliminating underlying disease factors.

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Authors' contributions

AS: Data collection, Investigation, Writing - Review & Editing; MS: Data collection, Investigation, Writing - Review & Editing; RJ: Data analysis, Investigation, Data

collection; AAH: Conceptualization, Methodology, Supervision, Writing - Review & Editing. All authors read and approved the final version.

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