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Etiology, clinical characteristics, and outcome of infective endocarditis: 10-year experience from a tertiary care center in Pakistan

Sara Salim Ali[1], Imran Ahmad Qureshi[2], Ahmed Ayaz[2], Ainan Arshad[3], Awais Farhad[4], Bushra Jamil[5], Muhammad Rizwan Sohail[6]

[1]Department of Pediatrics, University of Texas Medical Branch, Galveston, TX, USA; [2]Medical college, Aga Khan University, Karachi, Pakistan; [3]Department of Internal Medicine, Aga Khan University, Karachi, Pakistan; [4]Department of Cardiology, Aga Khan University, Karachi, Pakistan; [5]Department of Infectious Diseases, Aga Khan University, Karachi, Pakistan; [6]Department of Infectious Diseases, Baylor College of Medicine, Houston, TX, USA

Correspondence: Ainan Arshad, Aga Khan University, 1st floor, Faculty Office Building, Stadium Road, Karachi 74800, Pakistan. E-mail: ainan_arshad@hotmail.com

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Abstract

This study was conducted to assess the clinical characteristics, causative agents, complications, and outcomes of infective endocarditis (IE) among patients presenting to our tertiary care center over the last decade. This retrospective cohort study included all adult patients admitted to the Aga Khan University Hospital with the diagnosis of IE over a ten-year period from 2010 to 2020. Outcomes variables included complications during hospitalization, surgical intervention, mortality, and length of stay. We identified a total of 305 cases out of which 176 (58%) were males and 129 (42%) were females. The mean age of the patients was 46.9±18.8 years. 95 (31%) had prosthetic valves in place. *Staphylococcus aureus* was isolated in 54 (39%) patients followed by coagulase-negative *Staphylococcus* in 23 (17%). Echocardiography revealed vegetations and abscesses in 236 (77%) and 4 (1%) patients, respectively. The most common valvular complication was mitral valve regurgitation found in 26 (9%) patients, followed by tricuspid valve regurgitation in 13 (4%) patients and aortic valve regurgitation in 11 (3%) patients. Furthermore, 81 (27%) patients suffered from heart failure and 66 (22%) from a stroke during hospitalization. The mean hospital length of stay was 10.4±10.6 days. 64 (21%) patients required surgical repair and the overall mortality rate was 25%. Prosthetic valve endocarditis (OR = 3.74, 95% CI = 2.15-6.50, p<0.001), chronic kidney disease (OR = 2.51, 95% CI = 1.15-5.47, p=0.036), previous stroke (OR = 2.42, 95% CI = 1.18-4.96, p=0.026), and ischemic heart disease (OR = 3.04, 95% CI = 1.50-6.16, p=0.003) were significantly associated with an increased risk of mortality. In conclusion, our study provided valuable data on the clinical characteristics and outcomes of patients with IE in a developing country. *S. aureus* was the most common causative agent. Heart failure and stroke were the most common complications. The presence of prosthetic valves, history of chronic kidney disease, ischemic heart disease and previous stroke were associated with a significantly increased risk of mortality. Surgical management was not associated with improved outcomes.

Introduction

Despite improvements in diagnostic accuracy, medical therapy, and surgical techniques, in-hospital mortality remains high in

infective endocarditis (IE), approaching 20% or more, and remains essentially unchanged over the past 2 decades [1,2]. Medical innovations, an ageing population, and widespread changes in healthcare delivery in the last five decades have impacted the clinical spectrum of IE [3,4]. These include the increasing use of intracardiac devices, prosthetic heart valves, and complex medical comorbidities. Changes in antimicrobial prescription patterns have also led to alterations in microbial flora and infection with more resistant organisms [5-7].

IE is now associated with prolonged hospitalization due to complications such as heart failure, stroke, systemic embolization, and sepsis. These complications are associated with a higher mortality and impaired quality of life in patients who survive IE [8].

Most published data on IE is from medical centers in the developed countries. However, the epidemiology and microbiologic spectrum of IE are different in the South Asian population, compared to the western population. This study was conducted to assess the clinical characteristics, causative agents, and outcomes of IE patients over the last decade in a developing country with evolving healthcare system.

Materials and Methods

This retrospective cohort study included all adult patients admitted to the Aga Khan University Hospital with the diagnosis of IE over a ten-year period from 2010 to 2020. The study was approved by the Institutional Review Board at Aga Khan University (Ref no: 2019-1685-4104). We identified cases of IE through electronically coded medical records (International Classification of Diseases 9th revision with clinical modification, or ICD-9-CM). Blood culture results and echocardiography data of these patients was obtained from medical records to confirm cases of IE using modified Duke criteria and ACC guidelines [9].

The data of included patients was collected using medical records by the research team using a pre-approved case report form. Variables included demographics, comorbid conditions, hospitalization characteristics, laboratory, radiological findings, and outcome. Outcome variables included surgical management, length of stay, and mortality.

IBM SPSS 22 was used for data analysis. Continuous variables were reported as mean ± SD. Categorical variables were reported as counts and percentages. We compared characteristics between native valve and prosthetic valve endocarditis by using Student's *t*-test or Wilcoxon rank-sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables, based on cell counts. Multivariable logistic regression was used to determine independent factors associated with mortality after adjusting for potential confounding factors such as age, sex and comorbid conditions. A p-value less than or equal to 0.05 was considered significant.

Results

We identified a total of 305 cases out of which 176 (58%) were males and 129 (42%) were females. The mean age of the patients was 46.9 ± 18.8 years. Out of 305 patients, 95 (31%) had prosthetic valves in place. In our study population, 22 (7%) patients with native valves and 6 patients (2%) with prosthetic valves had a prior history of rheumatic heart disease (Figure 1). Baseline characteristics of all the included patients are presented in Table 1. Blood cultures were done for all 305 patients out of which 166 (54%) patients were reported as 'culture negative'. The remaining 139 (46%) were culture positive out of which 109 patients reported positive for Gram positive cocci. *Staphylococcus aureus* was isolated in 54 (39%) patients followed by Coagulase negative Staphylococcus in 23 (17%), Streptococci in 19 (14%) and Enterococci in 13 (9%). Microbiological and radiological characteristics of all patients are presented in Table 2. Echocardiography revealed vegetations and abscesses in 236 (77%) and 4 (1%) patients respectively. The most common valvular complication was mitral valve regurgitation found in 26 (9%) patients, followed by tricuspid valve regurgitation in 13 (4.3) patients and aortic valve regurgitation in 11 (3.6) patients. Furthermore, 81 (27%) patients suffered from heart failure and 66 (22%) from stroke. The overall average length of stay of patients was 10.4 ± 10.6 days. 64 (21%) patients required surgical repair and the overall mortality rate was 25%. Prosthetic valve endocarditis (OR = 3.74, 95% CI = 2.15-6.50, p=0.001), history of chronic kidney disease (OR = 2.51, 95% CI = 1.15-5.47, p=0.036), history of previous stroke (OR = 2.42, 95% CI = 1.18-4.96, p=0.026) and history of ischemic heart disease (OR = 3.04, 95% CI = 1.50-6.16, p=0.003) were significantly associated with an increased risk of mortality (Table 3).

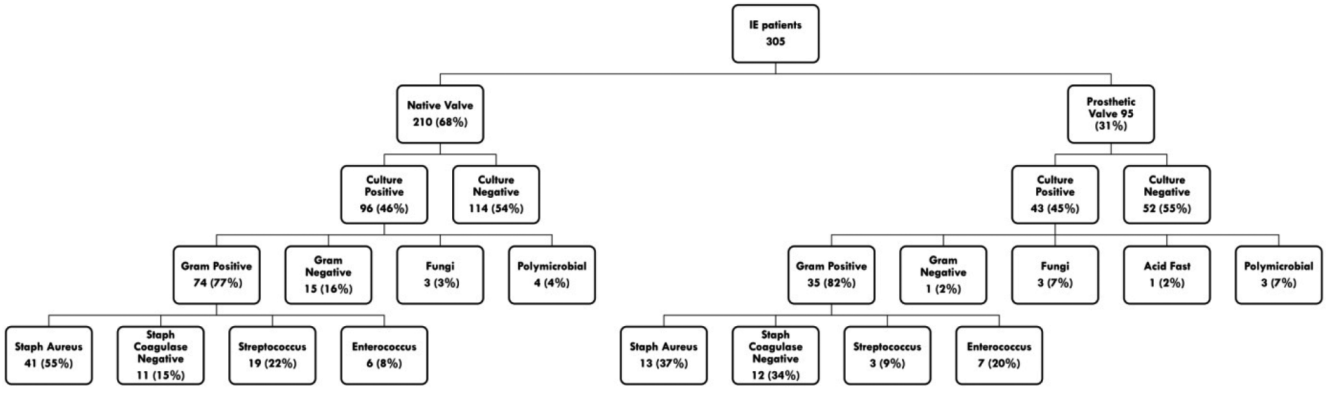

Figure 1. Patient inclusion and microbiologic etiology of IE (n=305).

Table 1. Overall demographic and clinical characteristics of IE patients (n=305).

Characteristics	Overall (n=305)	Native valve (n=210)	Prosthetic valve (n=95)	p-value
Mean age (years)	46.88±18.86	47.11±18.95	46.26±18.75	0.716
Gender				
Male	176 (57.7)	123 (58.6)	53 (55.8)	0.649
Female	129 (42.3)	87 (41.4)	42 (44.2)	
Comorbid conditions				
Diabetes	93 (30.5)	69 (32.9)	24 (25.3)	0.182
Hypertension	141 (46.2)	97 (46.2)	44 (46.3)	0.984
Chronic kidney disease	59 (19.3)	37 (17.6)	22 (23.2)	0.257
Malignancy	17 (5.6)	9 (4.3)	8 (8.4)	0.145
Stroke	71 (23.3)	51 (24.3)	20 (21.1)	0.536
History of cardiovascular diseases				
Ischemic heart disease	88 (28.9)	58 (27.6)	30 (31.6)	0.480
History of rheumatic heart disease	28 (9.2)	22 (10.5)	6 (6.3)	0.244
History of congenital heart disease	29 (9.5)	24 (11.4)	5 (5.3)	0.089
History of previous infective endocarditis	46 (15.1)	25 (11.9)	21 (22.1)	0.021
Outcome				
Length of stay (days)	10.44±10.64	9.63±8.97	12.24±13.51	0.087
Mortality	75 (24.6)	35 (16.7)	40 (42.1)	<0.001
Surgical repair	64 (21.0)	44 (21.0)	20 (21.1)	0.984
Complications				
Heart failure	81 (26.6)	53 (25.2)	28 (29.5)	0.438
Stroke	66 (21.6)	45 (21.4)	21 (22.1)	0.894

Discussion

In our study, we analyzed a total of 305 cases of IE over the past decade in a developing country with evolving healthcare system. The mean age of our patient population at the time of disease presentation was 46.9±18.8 years. This finding is on par with similar studies conducted in the region but lower than the patient population in the western world [10-15]. Previous literature suggests that the age of patients at presentation of this disease is influenced by the prevalence of uncorrected congenital heart disease and history of rheumatic heart disease, both of which serve as important predisposing risk factors for IE. In our study 29 cases (9.5%) were reported to have had history of congenital heart disease, while 28 (9.2%) had previous history of rheumatic heart disease. This is similar to a trend seen by Choudhary *et al.* in their study of a patient population in North India where a lower mean age of presentation correlated with an increased prevalence of these two risk factors [16].

Blood cultures were performed on all patients in our population, with a positive culture yield of only 46%. This value is much lower when compared to studies conducted on patients with IE in the west, which report a positive culture yield of about up to 80% in some studies [17,18]. One possible explanation for the low rate of culture-positive cases could be the widespread practice of self-medication with potent antibiotics, which are available over the counter, without relevant indications in our country. Other pre-analytical factors such as inadequate volume of blood drawn and infrequent sampling could also contribute to this finding [10].

S. aureus was the predominant causative pathogen in our population. This was in contrast to previous studies conducted in this region, where streptococci remained the most common isolated microorganism over the past two decades [10,11]. These findings closely reflect western trends, where *S. aureus* is the most common isolated pathogen [13,19-21]. Friedman and colleagues have suggested that improved healthcare provisions, rather than a lack of access to medical care, have resulted in the recent rise of *S. aureus* infections which are acquired during hospitalization (nosocomial infections), extensive outpatient procedures, intravenous therapy, wound care, hemodialysis, and residence in a nursing home or long-term care facility [22-24]. Other risk factors associated with this epidemiological transition can include an increasingly aging population, rising drug abuse, and increased use of prosthetic devices [14,20].

Timely diagnosis of IE and associated high morbidity and mortality continue to be a challenge despite advances in medical diagnostics and therapeutics [25]. Septic embolism, of which stroke is the most common, is a particularly feared complication of IE which is known to affect up to 50% of patients with IE around the world [26-29]. Our study reported a significantly lower number of patients suffering from this complication (25%). Additionally, stroke was also not associated with an increased risk of mortality. We believe that this could be explained by the younger patient population in developing countries which is in stark contrast to the developed world, where the increasing number of elderly patients with implanted intracardiac devices or prosthetic valves constitute a substantial and growing proportion of those affected.

Our study has potential limitations. Our institution is a tertiary referral centre and this could influence the complexity and microbiology of IE cases in our patient cohort. The retrospective nature of our study and reliance on ICD-9-CM codes for case finding are other potential limitations as we had to rely on existing data in electronic health records. We hypothesize that frequent use of outpatient antibiotics prior to admission is a major factor for the high rate of blood culture negativity in our patients. However, as this information was not consistently and reliably documented in patient records, we could not analyse the true impact of this prac-

tice. Lastly, diagnostic imaging serves as an important tool in the rapid diagnosis and management of IE with echocardiography being the first line imaging modality included in the modified Duke's Criteria [30]. While TEE serves as the gold standard for echocardiographic diagnosis of IE, it was performed in less than one third of the patients in our study population. TTE, being the more cost-effective and less-invasive procedure, was more commonly used in a resource limited setting such as ours.

Limitations

Our study has a few limitations. Firstly, we understand that ideally, in patients with equivocal findings on TTE, TEE or other imaging modalities, such as a PET scan, should have been performed. However, due to limited resources, this was not possible. Due to this, the number of patients with true endocarditis may have been underestimated. Secondly, we understand that high suspicion patients and those patients who were treated empirically for IE in the absence of findings of IE on TTE should have been included and reported separately. However, our dataset lacked sufficient granularity to identify those patients. Thirdly, lower rates of septic emboli in our study could be due to the lack of FDG-PET/CT to look for septic emboli. This was due to resource limitations in our setting.

Conclusions

Our study provided valuable data on the evolving clinical characteristics and outcomes of patients with IE in a developing country. *S. aureus* was the most common causative agent. Presence of prosthetic valves, history of chronic kidney disease, ischemic heart disease, and previous stroke were associated with a significantly increased risk of mortality in our study population. Mortality remained relatively high and surgical management did not improve outcomes.

Table 2. Microbiology and imaging characteristics (n=305).

Characteristics (n=305)	Overall (n=210)	Native valve (n=95)	Prosthetic valve
Culture negative	166 (54.1)	114 (54.4)	52 (55.2)
Culture positive	139 (46.3)	96 (46.1)	43 (45.4)
A) Gram positive	109 (78.4)	74 (77.1)	35 (81.4)
Staphylococcus aureus	54 (49.5)	41 (55.4)	13 (37.1)
Staph coagulase negative	23 (21.1)	11 (14.6)	12 (34.3)
Streptococcus	19 (17.5)	16 (21.6)	3 (8.6)
Enterococcus	13 (11.9)	6 (8.4)	7 (20.0)
B) Acid fast	1 (0.7)	0 (0.0)	1 (2.3)
Mycobacterium abscessus	1 (100.0)	0 (0.0)	1 (100.0)
C) Gram negative	16 (11.5)	15 (15.6)	1 (2.3)
Pseudomonas aeruginosa	4 (25.0)	4 (26.6)	0 (0.0)
Escherichia coli	6 (37.0)	6 (40.0)	0 (0.0)
Enterobacter species	3 (19.0)	3 (20.0)	0 (0.0)
Other gram negatives	3 (19.0)	2 (13.4)	1 (100.0)
D) Fungi	6 (4.3)	3 (3.1)	3 (7.0)
Candida	4 (66.6)	1 (33.3)	3 (100.0)
Other fungi	2 (33.3)	2 (66.6)	0 (0.0)
E) Polymicrobial	7 (5.0)	4 (4.2)	3 (7.0)
Cardiac imaging			
Trans-thoracic echo	277 (90.8)	193 (91.9)	84 (88.4)
Trans-esophageal echo	87 (28.5)	49 (23.3)	38 (40.0)
Findings on imaging			
Vegetation	236 (77.4)	161 (76.7)	75 (78.9)
Abscess	4 (1.3)	3 (1.4)	1 (1.1)
AV regurgitation	11 (3.6)	7 (3.3)	4 (4.2)
MV regurgitation	26 (8.5)	25 (11.9)	1 (1.1)
TV regurgitation	13 (4.3)	11 (5.2)	2 (2.1)

AV, aortic valve; MV, mitral valve; TV, tricuspid valve.

Table 3. Multivariate logistic regression of factors associated with mortality (n=305).

Characteristics	Odds ratio (95% CI)	p-value
Prosthetic valve	3.74 (2.15-6.50)	<0.001
History chronic kidney disease	2.51 (1.15-5.47)	0.036
History of previous stroke	2.42 (1.18-4.96)	0.026
History of ischemic heart disease	3.04 (1.50-6.16)	0.003

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