Comparison of Staphylococcus Aureus Endocarditis Risk Factors With Bacteremia

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Abstract

Introduction: Infective endocarditis (IE) is endothelial damage of the endocardium, which is caused by infection. The etiologic agents' highest mortality and morbidity rates are associated with staphylococcus aureus (S. aureus). Accordingly, the knowledge of different risk factors for IE caused by the S. aureus is necessary.

Material and methods: This study is an observational-analytical retrospective cohort study on 139 patients with staphylococcus aureus bacteremia (SAB), who referred to a cardiac center during 2011-2019. This study aimed to evaluate the risk factors in 48 patients with staphylococcus aureus endocarditis, who were selected from139 patients with S. aureus bacteremia.

Results: The mean age (±SD) of the patients is 56.61 (±16.58), and85 (61.2%) persons are male. Forty-eight patients (34.5%) are diagnosed with staphylococcus aureus endocarditis regarding Duke criteria. In this study, the following risk factors were significantly associated with *S. aureus* endocarditis: age (p=0.003), long-term bacteremia (p=0.041), prosthetic heart valve (p=0.016), pre-existing IE (p=0.048), and embolic events (p=0.039).

Conclusion: According to the findings, a significant number of patients with staphylococcus aureus bacteremia (SAB) have IE with different risk factors. Future studies with a larger sample size are recommended to detect IE risk factors.

Introduction

Infective endocarditis (IE) is defined as the infection-induced inflammation of the endocardial surface of the heart. The aggregation of activated platelets, fibrin, and pathogen causes the infective lesion in the endocardium (1, 2). The pathogeneses of the endocarditis are the endothelial damage of the endocardium leading to platelets adhesion and microbial adherence to the valvar tissue, often in patients with pre-existing structural heart diseases (3). The predictive factors of IE are valvar heart diseases, history of prior endocarditis, intravenous drug abuse, and hemodialysis (4). Because of the high mortality and morbidity rates of *S. aureus* endocarditis, its immediate diagnosis and treatment are of great importance (5). The late diagnosis and treatment of *S. aureus* endocarditis is associated with complications such as severe heart failure, supraventricular arrhythmias, and intracardiac disturbances (6). Trans-thoracic Echocardiography (TTE) and trans-esophageal Echocardiography (TEE) which exhibit the origin, complications, and outside endocardium spread of infection, are necessary for the early diagnosis of IE (7). Sinus tachycardia, low QRS voltage, bundle blocks, ST-segment elevation, atrial fibrillation, and supraventricular tachycardia are the electrocardiography (ECG) findings of IE (8). For the IE diagnosis, the above para-clinical findings and the Duke criteria are clinically recommended in some recent guidelines. In 1994, Durack et al. developed the Duke criteria for the diagnosis of the definite, possible and rejected IE. The Duke criteria include two major and five minor criteria, and the clinical diagnosis of definitive IE requires the presence of two major, one major and three minor, or five minor

criteria (9–12). Naber et al. showed that the Duke criteria are the more sensitive instrument for the IE diagnosis compared to paraclinical judgments, including ECG (13).

The most common microorganisms causing IE are streptococcus and staphylococcus aureus. Whenever *S. aureus* is the etiologic agent of the acute disease, the patient requires more intensive care and treatment (14). *S. aureus* is from the Micrococcaceae series and gram-positive cocci, which grows in a cluster. The *S. aureus* endocarditis occurs more in intravenous drug users, elderly patients, hospitalized patients, and patients with prosthetic valves, and its symptoms usually are rapid onset with high fever (15, 16). The *S. aureus* is in the environment, and as normal human flora of the skin and mucosa; however, it does not cause infection through healthy skin (17). Some healthcare workers are the carriers of *S. aureus* in their noses, and the microorganism does not cause damages to them; however, it may cause healthcare-associated infections in hospitals (18). The *S. aureus* can cause bacteremia and IE in healthy and immunologically-compromised individuals from communities and hospitals. Methicillin-resistant *S. aureus* (MRSA) species are fatal if mistreated; therefore, the detection of the bacteria's prevalence and risk factors is of paramount importance (19).

Berlin et al. (1995) declared that the high prevalence rate of IE was correlated with the increasing number of injecting drug users in the United States (20). In 1992, a group of scientists worked on the epidemiology of IE in the Netherlands, and the mitral valve prolapse with valvular endocarditis had the highest prevalence rate, followed by intravenous (IV) drug users. Moreover, the most common microorganisms inducing IE were streptococci, staphylococci, and enterococci (21). In a one-year survey in France in 2002, the annual incidence of IE was 30 cases per million, and streptococci was the highest etiologic agent of bacterial IE (22). In 2007, Letaief et al. represented a ten-year survey indicating that rheumatic valvar disease was the leading risk factor for IE among patients for whom staphylococcus was the most common microorganism etiology (23). However, in Spain, IE is currently rare in older adults with no pre-existing heart problems. Among those in close contact with the healthcare system, streptococcus and staphylococcus are the two most frequent IE species (24). Regarding the poor prognosis and high mortality and morbidity rates of *S. aureus* IE, this study aimed to determine the frequency of various risk factors for *S. aureus* IE in patients with staphylococcus aureus bacteremia.

Material And Method

This study was an observational-analytical retrospective cohort study on 200 patients referred to the Shahid Rajaee Cardiovascular, Medical & Research Center in Tehran, Iran, during 2011-2019. The participants' demographic and clinical information, including age, gender, pre-existing IE, electronic heart device usage, existence of cardiac prosthetic valves, IV drug usage, catheter-related, and dialysis, were collected from all patients' records. Duke criteria were used for the clinical diagnosis of IE and the TTE-based paraclinical diagnosis. Regarding the Duke criteria, the clinical diagnosis of definitive IE requires the presence of two major, one major and three minor, or five minor criteria. Three blood cultures with the minimum and maximum of one-hour and 24-hour intervals according to Duke criteria, if the results of the primitive cultures were negative after 24-48 hours, 2 or 3 more cultures including lysis-centrifuge culture

were prepared and send to the laboratory for detecting specific cultural microorganisms. Finally, the logistic regression model was used to detect the risk factors of IE in this study. The exclusion criteria were being discharged during the last 72 hours, aged below 18 years, death outcome, no TTE performed for the IE diagnosis, being transferred to other centers, and undergoing palliative care, according to which 61 patients were excluded from this study, and 139 patients were included. All the patients referred to staphylococcus aureus bacteremia (SAB) and SAB+IE were studied for the risk factors.

The collected data was imported to Statistical Package for the Social Sciences (SPSS) software version 25 to be analyzed using descriptive and inferential statistics. Regarding the descriptive statistics, mean and standard deviation (SD) were defined for quantitative variables, and absolute and relative abundance were performed for qualitative variables. In the inferential section, Kolmogorov-Smirnov and Shapiro-Wilk tests were used. The logistic regression model was also used to detect the risk factors of staphylococcus aureus endocarditis. In this study, $p < 0.05$ was set as the significance level. This study was approved by the ethics Committee of the Islamic Azad University of Medical Sciences (Code: IR.IAU.TMU.REC1398.132), and we confirm that all experiments were performed in accordance with relevant guidelines and regulations.

Results

In this study, out of 139 patients, 48(34.5%) patients had staphylococcus aureus endocarditis. The participants were 18-95 years old, with the mean age (±SD) of 56.61 (±16.58) years, and 57.3% of patients are 51-70 years old. Moreover, 85 (61.2%) patients were male, 33 (39.3%) patients had right side IE, 42 (50%) had left side IE, and 9 (10.7%) patients had full heart involvement. Further, 48 (34.5%) patients were diagnosed with definite IE regarding Duke criteria. Long-lasted bacteremia (>72 hours) was observed in 38 (27.3%) patients. The origins of SAB were community-acquired (n= 51, 36.7%), nosocomial (n=40, 27.8%), healthcare-acquired (n=42, 30.2%), and unknown (n=6, 4.3%).

Among the 139 patients with SAB, 12 (6.8%) patients had pre-existed embolic events, 24 (17.3%) patients used electronic heart devices, 80 (57.6%) patients had cardiac prosthetic valves, 2 (1.4%) patients were IV drug abusers, 11 (7.9%) patients had previous osteomyelitis, 11 (7.9%) patients were previously hospitalized for IE, none of the patients had any first-degree relative with a history of IE, 7 (5%) were dialysis patients, 54 (38.8%) patients had diabetes, 2 (1.4%) patients had a history of cancers, 32 (23%) patients suffered from catheter-using infection, and 18 (36.7%) patients were diagnosed with MRSA IE.

In this study, *S. aureus* endocarditis was more frequent in patients aged below 50 years compared to those aged 50 years or above (*p*=0.003). Men were more susceptible to SAB+IE (*p*=0.480). The frequencies of different risk factors for Staphylococcus aureus endocarditis were as follows: 18 patients with long term bacteremia (*p*=0.041), nine patients with electronic heart devices (*p*=0.454), 34 patients with prosthetic cardiac valves (*P*=0.016), seven patients with pre-exists endocarditis (*p*=0.048), two IV drug abusers (*p*=0.118), one patient with previous embolization history (*p*=0.039), three patients with a

history of osteomyelitis (p=0.434), two patients with dialysis (p=0.542), one patient with a history of cancer (p=0.573), and eight patients using catheter (p=0.139) (Table 1).

Table 1
The prevalence of risk factors in this study.

Variables	Situation	Value	S. aureus IE		P-Value
			-	+	(Fisher's Exact Test)
Age	<50	Quantity	18	21	0.003
		Percentage	46.2%	53.8%	
	≥50	Quantity	72	27	
		Percentage	72.7%	27.3%	
Sexuality	Male	Quantity	55	30	0.480
		Percentage	64.7%	35.3%	
	Female	Quantity	36	18	
		Percentage	66.7%	33.3%	
Long-term Bacteremia	-	Quantity	71	30	0.041
		Percentage	70.3%	29.7%	
	+	Quantity	20	18	
		Percentage	52.6%	47.4%	
Electronic Heart Devices	-	Quantity	76	39	0.454
		Percentage	66.1%	33.9%	
	+	Quantity	15	9	
		Percentage	62.5%	37.5%	
Prosthetic Heart Valves	-	Quantity	45	14	0.016
		Percentage	76.3%	23.7%	
	+	Quantity	46	34	
		Percentage	57.5%	42.5%	
IV Drug Use	-	Quantity	91	46	0.118
		Percentage	66.4%	33.6%	
	+	Quantity	0	2	
		Percentage	0.0%	100.0%	
Preexisting IE	-	Quantity	87	41	0.048

IE = Infective Endocarditis. SAB= Staphylococcus aureus bacteremia

		Percentage	68.0%	32.0%	
	+	Quantity	4	7	
		Percentage	36.4%	63.6%	
Embolic Event	-	Quantity	80	47	0.039
		Percentage	63.0%	37.0%	
	+	Quantity	11	1	
		Percentage	91.7%	8.3	
Osteomyelitis	-	Quantity	83	45	0.434
		Percentage	64.8%	35.2%	
	+	Quantity	8	3	
		Percentage	72.7%	27.3%	
Dialysis	-	Quantity	86	46	0.542
		Percentage	65.2%	34.8%	
	+	Quantity	5	2	
		Percentage	71.4%	28.6%	
Cancer	-	Quantity	90	47	0.573
		Percentage	65.7%	34.3%	
	+	Quantity	1	1	
		Percentage	50.0%	50.0%	
Catheter-Related	-	Quantity	67	40	0.139
		Percentage	62.6%	37.4%	
	+	Quantity	24	8	
		Percentage	75.0%	25.0%	
IE = Infective Endocarditis. SAB= Staphylococcus aureus bacteremia					

Discussion

In the present retrospective case-control study, out of 139 Staphylococcus aureus bacteremia patients, 48 (34.5%) patients had staphylococcus aureus endocarditis. The rising incidence of Staphylococcus aureus endocarditis can be associated with the following risk factors. In our study, the relationship among some risk factors (namely sexuality, electronic heart device, IV drug abuse, osteomyelitis, dialysis, cancer, and

catheter-related) was not significant for *S. aureus* (SA)+IE; however, age, long-term bacteremia, prosthetic heart valve, pre-exists IE, and embolic events were significantly associated with SAB+IE.

According to Mylonakis et al., men were more likely for SAB+IE than women. In their study, the risk factors were native-valves endocarditis SAB, and IV drug abuse -the most common risk factor for SAB+IE in younger adults. Other risk factors were poor dental hygiene, long-term hemodialysis, and diabetes mellitus. In the present study, sexuality, however, does not play a significant role in SAB+IE, and the prevalence of the mentioned risk factors was lower and non- significant. The inconsistency of the findings might have been caused by the small sample size and the patients' mean age. In general, Mylonakis et al. mentioned that the prosthetic valves and nosocomial acquired endocarditis were the possible causes of SAB+IE. The prevalence of the prosthetic valve in their study was compared to that of our study (1). In two different studies by Palraj et al. and Elisabeth Holden et al. in the United Kingdom, cardiac devices were reported as the most common IE risk factor in patients with SAB. However, in the present study with a different sample size and mean age, electronic cardiac devices were not a significant risk factor for SA+IE (25, 26). In our study, patients with hemodialysis revealed no significant association with SA+IE. Dr. Robinson et al. indicated the necessity of prophylaxis treatment for IE in patients undergoing hemodialysis.

In another study in Taiwan, hemodialysis was introduced as an essential attribute of IE. In their study, Mccarthy et al. observed that, consistent with our findings, IE was infrequent in 20 hemodialysis patients, and that the most common etiologic agent of their research was *S. aureus* (27–29). We also observed no significant relationship between IV drug-abusing and IE; however, in a survey in New York on 54 patients aged above 18 years, the increase in IV drug-abusing was found to be associated with the recent rise in IE (30). Regardless of our survey, Speechly-Dick and Swanton highly recommended that all IE patients were studied for osteomyelitis. In Tamura's study on 58 patients with IE, IE was associated with vertebral osteomyelitis. However, Salvador et al. worked on 91 SAB+IE and discovered no correlation between osteomyelitis and SAB+IE (31–33). The frequency of cancer in the IE patients was not significant in our study. In their study on 161 patients with cancer, Fernández-Cruz et al. reported that the most common etiologic agent of IE was streptococcus. Kim studied 170 patients with cancer and found out that the most common etiologic agent of IE was staphylococcus (34, 35). Catheter-related IE was studied in the present study, and the results revealed no significant correlation between IE and catheters. This is, while Chang et al. recommends the investigation of IE in catheter-related patients (36).

Similar to the present study, Finkelstein et al. studied the risk factors for 303 patients with SAB+IE and reported that long-term bacteremia was related to IE significantly (37). In Rasmussen's et al. study, echocardiography was recommended in patients with SAB to look for definite or possible IE (38). They observed that the prosthetic heart valve was closely connected to IE, and the artificial valves mentioned above were associated with IE in other similar surveys (33, 39). As Warren and Butany explained, implanting prosthetic heart valve as a foreign object causes inflammatory cell exudation, thereby inducing endocarditis. Further, the infection from normal flora of the skin leads to IE (40). In line with the findings of our survey, Hogevik et al. declined the embolic events before or after IE; however, the

significant amount in Hogevik's work was different from ours. In this regard, the presence of vegetation on TEE is a predictive factor of embolic events in patients with IE (41, 42). This study showed that patients with pre-existing IE would go through new IE. Generally, previous IE was associated with the future possibility of IE, as stated by Netzer et al., who followed up 212 pre-existing IE patients (43). In this regard, age was a variable with the strongest relationship with IE. We observed that IE was more common in patients aged below 50 years.

Conclusion

The present study revealed that many patients with SAB have IE and risk factors for SA+IE; hence, they should perform Echocardiography in all patients with SAB to diagnose IE. In this study, significant risk factors were aged below 50 years, pre-existing IE, prosthetic heart valve, embolic events, and long-term bacteremia. Further studies with a large sample size are recommended to rule out IE in patients referred with S. aureus bacteremia and its risk factors.

Limitations Of The Study

1. The sample size is relatively small.
2. The age under 18 years old need to be included

Declarations

Ethics approval and consent to participate:

This study was approved by the ethics Committee of the Islamic Azad University of Medical Sciences (Code: IR.IAU.TMU.REC1398.132).

Authors' contributions:

Majid Khani Ghale gathered the required information. The manuscript was authored under supervision of Dr. Mehrangiz Zangeneh and Dr. Monireh Kamali. Yasamin Khosravani-Nezhad coauthored the manuscript. All the authors have reviewed the manuscript.

Declaration of interests:

We declare no conflicts of interest.

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