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Comparison of risk factors in patients with positive and negative *Staphylococcus aureus* infective endocarditis: A cross-sectional study

Majid Khani Ghale[1] , Monireh Kamali[2] , Yasamin Khosravani-Nezhad[1], Shirin Manshouri[2], Akram Gholamzadeh[3], Mehrangiz Zangeneh[1,4*]

[1]Department of Infectious Diseases, Faculty of Medicine, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran
[2]Cardiovascular Research Center, Rajaie Cardiovascular Institute, Iran University of Medical Sciences, Tehran, Iran
[3]Department of Biotechnology, Islamic Azad University, Medical Sciences Branch of Tehran, Tehran, Iran
[4]Reproductive Biomedicine Research Center, Royan Institute Reproductive Biomedicine, ACECR, Tehran, Iran

*Corresponding Author: Mehrangiz Zangeneh, Email: zangeneh4@yahoo.com

Summary

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

Methods: This analytical cross-sectional study included 200 patients referred to the Shahid Rajaee Cardiovascular, Medical, and Research Center from 25 November 2011 to 12 December 2019. A total of 139 patients with *S. aureus* bacteremia (SAB) were analyzed, with 48 diagnosed with endocarditis. Data were evaluated using SPSS software, employing descriptive and inferential statistics, including logistic regression, with a significance level set at $P < 0.05$.

Findings: The mean age of the patients is (56.61 ± 16.58), and 85 (61.2%) persons are male. Forty-eight patients (34.5%) are diagnosed with *S. aureus* endocarditis according to 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 SAB have IE with different risk factors. Future studies with a larger sample size are recommended to detect IE risk factors.

Keywords: *Staphylococcus aureus*, Infective endocarditis, Risk factors, Bacteremia

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 pathogens causes the infective lesion in the endocardium.[1,2] The pathogenesis of endocarditis is the endothelial damage of the endocardium, leading to platelet adhesion and microbial adherence to the valvular tissue, often in patients with pre-existing structural heart diseases.[3] The predictive factors of IE are valvular heart disease, history of prior endocarditis, intravenous drug abuse, and hemodialysis.[4] Because of the high mortality and morbidity rates of *Staphylococcus aureus* endocarditis, its immediate diagnosis and treatment are of great importance.[5] The late diagnosis and treatment of *S. aureus* endocarditis are 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 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 a 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] The *S. aureus* is from the *Micrococcaceae* series and gram-positive cocci, which grow in clusters. 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 carriers of *S. aureus* in their noses, and the microorganism does not cause damage 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 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 *S. aureus* bacteremia.

Methods

This analytical cross-sectional study was conducted on 200 patients referred to the Shahid Rajaee Cardiovascular, Medical & Research Center in Tehran, Iran, from 25 November 2011 to 12 December 2019. We collected demographic and clinical data, including age, gender, pre-existing IE, electronic heart device usage, presence of cardiac prosthetic valves, intravenous drug use, catheter-related infections, and dialysis, from patient records. The diagnosis of IE was established using the Duke criteria, requiring either two major criteria, one major and three minor criteria, or five minor criteria for definitive diagnosis. Blood cultures were performed according to the Duke criteria, with three cultures taken at one-hour to 24-hour intervals. If initial cultures were negative after 24-48 hours, additional lysis-centrifuge cultures were prepared for laboratory analysis to detect specific microorganisms.

Of the initial cohort, 61 patients were excluded based on specific criteria: discharge within the last 72 hours, age under 18 years, death outcome, lack of TTE for IE diagnosis, transfer to other centers, and undergoing palliative care. Ultimately, 139 patients with *S. aureus* bacteremia (SAB) were included, with 48 diagnosed with *S. aureus* endocarditis. We compared the SAB + IE patients with those without IE to identify significant risk factors associated with IE in SAB patients.

Statistical analysis

The data were analyzed utilizing SPSS software (version 25), employing both descriptive and inferential statistical methods. Normality of data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Logistic regression analysis was conducted to identify potential risk factors associated with Staphylococcus aureus endocarditis. A significance threshold of $P < 0.05$ was applied throughout the analysis.

Results

In this study, out of 139 patients, 48 (34.5%) patients had *S. aureus* endocarditis. The participants were 18-95 years old, with the mean age ($\pm$ SD) of 56.61 ($\pm$ 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 origin of SAB was 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 *S. 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).

Discussion

In the present study, out of 139 *S. aureus* bacteremia patients, 48 (34.5%) patients had *S. aureus* endocarditis. The rising incidence of *S. 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 and Calderwood, 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 and Calderwood 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 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 and Steckelberg 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[31] highly recommended that all IE patients were studied for

osteomyelitis. In Tamura's study[32] 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.[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[34] reported that the most common etiologic agent of IE was *Streptococcus*. Kim et al studied 170 patients with cancer and found out that the most common etiologic agent of IE was *Staphylococcus*.[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 and colleagues' 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 Jegatheeswaran 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 and colleagues' 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. Limitations of the study consisted of the sample size was relatively small and the age under 18 years old needed to be considered.

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.

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
		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.

patients who consented to use their information in this study.

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