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Clinical Features and Risks Associated with In-hospital Mortality in Patients with Infective Endocarditis at A Medical Center in Central Taiwan from 2012 to 2016 – A Retrospective Analysis

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Abstract

To outline the clinical features and identify risks associated with in-hospital mortality in patients with infective endocarditis. Adult patients who were diagnosed with definite infective endocarditis (IE) from January 2012 to December 2016 were retrospectively analyzed. A total of 87 patients, including 57 (65.5%) men and 30 (34.5%) women, were included, with a mean age of 54.1±16.6 years (ranging from 18 to 85 years). Fifty (57.5%) patients had mitral valves involvement. Among the 87 patients, 32 (36.8%) had IE by *Staphylococcus aureus*, while 14 (16.1%) patients had IE by methicillin-resistant *Staphylococcus aureus* (MRSA). Liver cirrhosis (Odd Ratio [OR] 18.38, 95% Confidence Interval (CI) 2.46-137.20, p=0.007) and diabetes mellitus (OR 4.52, 95% CI 1.01-20.30, p=0.049) were both associated with IE by MRSA. Twenty of the 87 patients died during the hospitalization, with the in-hospital mortality rate being 23.0%. The age older than 65 years was associated with an increased in-hospital mortality rate (OR 5.81, 95% CI 1.62-20.87, p=0.007). Infective endocarditis remains a lethal disease, particularly in the elderly. Clinicians should not underestimate the prevalence of MRSA infection in patients with infective endocarditis. (J Intern Med Taiwan 2018; 29: 309-316)

Key Words: Mortality, Methicillin-resistant, Infective endocarditis

Introduction

Infective endocarditis is associated with a high mortality rate[1,2,3]. Risks previously reported to be associated with mortality amongst patients with IE in Taiwan included older age, male gender, diabetes mellitus, malignancy, renal insufficiency, elevated white blood cell counts, nosocomial infection, Staphylococcus infection, neurological complications, heart failure, respiratory failure, and shock[4-9]. Despite the progress being made in both diagnosis and treatment, the overall mortality rate remains high[4-10]. To improve outcomes, the identification of patients who are at a high risk of mortality is important.

In addition, in most part of the world, *Staphylococcus aureus* is now the most common cause of infective endocarditis, which is attributed to the global presence of risk factors for *Staphylococcus aureus* infection, such as intravenous drug use, health care contact, and invasive procedures[11-13].

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Rates of infections by MRSA also increased dramatically, which have complicated the treatment of IE by *Staphylococcus aureus*[14,15]. Updated knowledge of contemporary microbiology is critical in the management of IE.

We conducted this retrospective study in order to describe the epidemiological features and clinical characteristics of infective endocarditis in a tertiary-care medical center in central Taiwan, and to also identify the risks associated with in-hospital mortality.

Materials and methods

Patients

From January 2012 to December 2016, a total of 420 patients who were admitted to Taichung Veterans General Hospital with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding of ICD-9-CM 421.0, ICD-9-CM 421.1, ICD-9-CM 421.9 , ICD-9-CM 424.90, ICD-9-CM 424.91, ICD-9-CM 424.99, ICD-9-CM 036.42, or ICD-9-CM 112.81, or the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) coding of ICD-10-CM A39.51, ICD-10-CM I33.9, ICD-10-CM I33.0, ICD-10-CM B37.6, ICD-10-CM I38, or ICD-10-CM I39, were identified. We reviewed those medical charts. The inclusion criteria are patients who fulfilled the modified Duke criteria of definite IE, including the pathological criterion, two major clinical criteria, and one major and two minor clinical criteria.

The exclusion criteria are patients younger than 18 years of age and patients who only met possible criteria or did not meet the modified Duke criteria as proposed by Li et al[16].

Methods

The following variables were included for analysis: age, gender, diabetes mellitus, hypertension, coronary artery disease, baseline creatinine, end stage renal disease, liver cirrhosis, history of intravenous drug use, presence of prosthetic valves, vegetation size (in diameters), blood microorganism and their susceptibility profile, major embolic events (evidenced on computed tomography), surgery during the same admission, and surgical indication.

Statistical analyses

We used both the chi-square test and Fisher's exact test to compare the categorical variables between patients at age older than 65 years and patients younger than 65 years. We used logistic regression analysis to identify risks associated with IE by MRSA and in-hospital mortality. Variables which were found to be significantly associated with IE by MRSA and in-hospital mortality through bivariable logistic regression analysis were included in the multivariable logistic regression analysis. The results were regarded as statistically significant if the p value was < 0.05. We used PASW Statistics for Windows, Version 18.0, to perform the analyses.

Results

A total of 87 patients, including 57 (65.5%) men and 30 (34.5%) women, met the inclusion criteria. Thirty-seven (42.5%) patients met the pathological criterion, 35 (40.2%) met two major clinical criteria, while 15 (17.2%) met one major and two minor clinical criteria. The mean age was 54.1 ± 16.6 years (ranging from 18 years to 85 years). Twenty-four (27.6%) of the 87 patients were older than 65 years of age. More of the elderly patients experienced hypertension, had baseline serum creatinine levels of more than 2 mg/dl or end stage renal disease, and IE by *Staphylococcus aureus*, with fewer of them undergoing surgery during the same admission, when compared to patients younger than 65 years of age. (Table 1)

Seventy-six (87.4%) of the 87 patients had native valve endocarditis, while 11 (12.6%) of the 87 patients had prosthetic valve endocarditis. Five

(5.7%) of the 87 patients had a history of intravenous drug use, while one (1.1%) of them had HIV infection.

Seventy-six (87.4%) of the 87 patients had left-sided infective endocarditis, while 11 (12.6%) of the 87 patients had right-sided infective endocarditis. Mitral valves were in first place in 50 (57.5%) patients, followed by aortic valves in 24 (27.6%) patients and tricuspid valves in 8 (9.2%) patients. Two (2.3%) patients had concurrent mitral valves and aortic valves involvement. In addition, two (2.3%) patients had vegetation on the interventricular septum in their right ventricle, while one (1.1%) patient had vegetation attached to the pacing wire in her right atrium. Among the five patients with a history of intravenous drug use, four (80%) of them had right-sided infective endocarditis.

Blood cultures were performed on all patients and were positive in 79 (90.8%) patients. The most common pathogen was *Staphylococcus aureus* in 32 (40.5%) of 79 patients, including Methicillin-sensitive *Staphylococcus aureus* (MSSA) in 18 (56.2%) of 32 patients and MRSA in 14 (43.8%) of 32 patients, followed by Streptococci in 31 (39.2%) patients. Additionally, Staphylococci other than *Staphylococcus aureus* was found in seven (8.9%) patients, and Enterococci in three (3.8%) patients. Other pathogens included *Klebsiella pneumoniae* in two (2.5%) patients, *Pseudomonas aeruginosa* in one (1.3%) patient, *Enterobacter aerogenes* in one (1.3%) patient, *Sphingomonas paucimobilis* in one (1.3%) patient, and *Candida albicans* in one (1.3%)

Table 1. Comparison of clinical characteristics between patients at age older than 65 years and younger than 65 years

Characteristic	Age > 65 years (n=24)	Age ≦ 65 (n=63)	p value
Demography data			
Male gender	13 (54.2%)	44 (69.8%)	0.169
Comorbidities			
Diabetes mellitus	8 (33.3%)	9 (14.3%)	0.068
Hypertension	16 (66.7%)	24 (38.1%)	0.017*
Coronary artery disease	5 (20.8%)	4 (6.3%)	0.107
Chronic kidney disease[a]	11 (45.8%)	12 (19.0%)	0.011*
Liver cirrhosis	4 (16.7%)	3 (4.8%)	0.088
IVDU[b]	0 (0%)	5 (7.9%)	0.316
Prosthetic valves	6 (25%)	5 (7.9%)	0.064
Vegetation size in diameter			0.207
< 1 cm	10 (41.7%)	18 (28.6%)	
>= 1 cm, < 2 cm	11 (45.8%)	26 (41.3%)	
>= 2 cm	3 (12.5%)	19 (30.2%)	
Blood microorganism			
Staphylococcus aureus	15 (62.5%)	17 (27.0%)	0.002*
Not aureus Staphylococci	2 (8.3%)	5 (7.9%)	
Viridans streptococci	3 (12.5%)	24 (38.1%)	
Others[c]	4 (16.7%)	17 (27.0%)	
Surgery in hospitalization	5 (20.8%)	44 (69.8%)	<0.001*
Outcome			
Embolic events	12 (50%)	21 (33.3%)	0.152
In-hospital mortality	13(54.2%)	7 (11.1%)	<0.001*

[a] Creatinine more than 2 mg/dl or end stage renal disease.
[b] Intravenous Drug User.
* $p<0.05$.
[c] Including other streptococci, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter aerogenes, Sphingomonas aucimobilis, Candida albicans* and no pathogen identified.

patient. Among the five patients with a history of intravenous drug use, four (80%) of them had IE by *Staphylococcus aureus*. Among the eleven patients with prosthetic valves endocarditis, six (54.5%) patients had IE by *Staphylococcus aureus*. (Table 2)

An univariate analysis revealed that age older than 65 years (OR 3.29, 95% CI 1.01-10.72, p=0.048), diabetes mellitus (OR 4.23, 95% CI 1.23-14.57, p=0.022), baseline serum creatinine levels of more than 2 mg/dl or end stage renal disease (OR 5.16, 95% CI 1.55-17.14, p=0.007), and liver cirrhosis (OR 19.72, 95% CI 3.32-117.00, p=0.001) were associated with IE by MRSA. A multivariate analysis revealed that both diabetes mellitus (OR 4.52, 95% CI 1.01-20.30, p=0.049) and liver cirrhosis (OR 18.38, 95% CI 2.46-137.20, p=0.005) were associated with IE by MRSA. (Table 3)

Thirty-three (37.9%) of the 87 patients experienced major embolic events, with a total of 36 embolic events being identified, including 22 (61.1%) cerebral embolic events, eight (22.2%) pulmonary embolic events, five (13.9%) splenic embolic events, and one (2.8%) renal embolic event. Twenty-two (61.1%) embolic events occurred prior to the diagnosis of infective endocarditis, eight (22.2%) embolic events occurred within one week after the diagnosis of infective endocarditis, and three (8.3%) embolic events occurred between one and two weeks after the diagnosis of infective endocarditis.

Surgery was performed during the same admission on 49 (56.3%) patients, with five (10.2%) of the patients dying post-operatively. These five patients died on post-operation day 8, 12, 22, 44, and 74, respectively. The most common surgical indication was heart failure in 28 (57.1%) of the patients, followed by uncontrolled infection in 13 (26.5%) patients and finally prevention of embolism due to a large vegetation size in eight (16.3%) of the patients.

Twenty of the 87 patients died during hospitalization, implying an overall mortality rate of 23.0%. Amongst 20 of the patients who experienced in-hospital mortality, fourteen (70%) of them died of uncontrolled infection from multiple organ dysfunction due to IE. Additionally, three (15%) patients died of hemorrhagic stroke due to septic emboli from IE, while two (10%) patients died of heart failure.

Table 2. Microbiology of patients with infective endocarditis

	Total (n=87)	Native valve endocarditis (n=76)	Prosthetic valve endocarditis (n=11)
Staphylococcus aureus	32 (36.8%)	26 (34.2%)	6 (54.5%)
MSSA	18 (20.7%)	16 (21.1%)[a]	2 (18.2%)
MRSA	14 (16.1%)	10 (13.2%)	4 (36.4%)
Other staphylococci	7 (8.0%)	6 (7.9%)	1 (9.1%)
Viridans streptococci	27 (31.0%)	16 (21.1%)	1 (9.1%)
Other streptococci	4 (4.6%)	3 (3.9%)	1 (9.1%)
Enterococci	3 (3.4%)	2 (2.6%)	1 (9.1%)[b]
Others	6 (6.9%)	6 (7.9%)	0 (0%)
Klebsiella pneumoniae	2 (2.3%)	2 (2.6%)	
Pseudomonas aeruginosa	1 (1.1%)	1 (1.3%)	
Enterobacter aerogenes	1 (1.1%)	1 (1.3%)	
Sphingomonas aucimobilis	1 (1.1%)	1 (1.3%)	
Candida albicans	1 (1.1%)	1 (1.3%)	
No pathogen identified	8 (9.2%)	8 (10.5%)	0 (0%)

[a] Including four patients with a history of intravenous drug use.
[b] Including one patient with a history of intravenous drug use.

Univariate analysis revealed that age older than 65 years (OR 9.46, 95% CI 3.07-29.08, p<0.001), baseline serum creatinine levels at more than 2 mg/dl or end stage renal disease (OR 3.10, 95% CI 1.07-8.94, p=0.037), liver cirrhosis (OR 10.83, 95% CI 1.91-61.31, p=0.007), and IE by *Staphylococcus aureus* (OR 4.69, 95% CI 1.62-13.56, p=0.004) were all associated with an increased in-hospital mortality, and that surgery during the same admission (OR 0.17, 95% CI 0.06-0.54, p=0.002) was associated with a decreased in-hospital mortality. Multivariate analysis revealed that age older than 65 years was associated with an increased in-hospital mortality, with an OR of 5.81 (95% CI 1.62-20.87, p=0.007). (Table 4)

Discussion

In this retrospective study, we have reported on the main clinical features in 87 patients diagnosed with IE during the five-year period encompassing 2012 to 2016. We identified age older than 65 years to be the main contributor to in-hospital mortality.

Chen et al[4] reported Viridans streptococci to be the main causative pathogen for infective endocarditis in Changhua Christian Hospital during the years 1989 to 1999. However, studies which occurred in the years following reported *Staphylococcus aureus* as being the most common causative pathogen in Taiwan[5-8,10]. In fact, in most parts of the world, *Staphylococcus aureus* is now the most common cause of IE[13]. We had a similar finding in that *Staphylococcus aureus* was the leading cause of infective endocarditis. Additionally, we also discovered that *Staphylococcus aureus* constituted for 80% of identified pathogens in patients with a history of intravenous drug use, and more than half in patients with prosthetic valves endocarditis. Accordingly, the empiric antibiotics choice for the treatment of infective endocarditis should include spectrum of activity against *Staphylococcus aureus*, particularly those with a history of intravenous drug use and those with prosthetic valve endocarditis.

The emergence of MRSA as a common pathogen has added new challenges in infection management. Chen et al[4] reported MRSA to be responsible for only 1.7% (one of 58 patients) of IE in their

Table 3. Multivariable regression analysis of risks associated with IE by MRSA

	Odds ratio	95% confidence interval	P value
Age older than 65 years	1.56	0.38-6.42	0.537
Diabetes mellitus	4.52	1.01-20.30	0.049*
Chronic kidney disease[a]	3.79	0.93-15.36	0.062
Liver cirrhosis	18.38	2.46-137.20	0.005*

*p<0.05.
[a] Creatinine more than 2 mg/dl or end stage renal disease.

Table 4. Multivariable regression analysis of risks associated with in-hospital mortality

	Odds ratio	95% confidence interval	P value
Age older than 65 years	5.81	1.62-20.87	0.007*
Chronic kidney disease[a]	1.42	0.40-5.04	0.588
Liver cirrhosis	5.29	0.66-42.28	0.116
IE by Staphylococcus aureus	1.51	0.38-6.06	0.556
Surgery during the same admission	0.54	0.13-2.23	0.390

[a] Creatinine more than 2 mg/dl or end stage renal disease.
*p<0.05.

study which was conducted in a medical center in central Taiwan during the period from January 1989 to September 1998. However, studies performed in Taiwan in the following years revealed MRSA to be a common cause of infective endocarditis[5,7-10], constituting as high as 22.0% (44 of 200 patients) of IE in the study by Wu et al[8]. The only exception found was in the study by Hsieh et al[9], in which MRSA was responsible for 3.6% (two of 55 patients) of infective endocarditis in eastern Taiwan during the period from January 2007 and December 2010. In our study, MRSA was the cause of 16.1% (14 of 87 patients) of IE, and the prevalence was particularly high in patients with diabetes mellitus (35.3%, six of 17 patients), along with patients diagnosed with liver cirrhosis (71.4%, five of seven patients).

Among 14 patients with IE by MRSA, three (21.4%) had catheter-related bloodstream infection, and one (7.1%) had preceding mitral valve replacement which was complicated with sternal wound infection by MRSA. Meanwhile, none of 18 patients with IE by MSSA had preceding infection foci.

Among six patients with diabetes mellitus and five patients with liver cirrhosis who had IE by MRSA, the patient number is to small to identity the possibility of nosocomial infection in these patients. Further study by molecular characterization is required to confirm the origin of MRSA infection.

Durante-Mangoni et al[3] found that largest relative increase in the incidence of infective endocarditis occurred in the elderly population, where elderly patients carried the risk of endocarditis at a 4.6 times higher rate than the general population. Lower rates of surgical treatment, along with a high mortality rate comprised the most prominent features amongst elderly patients with infective endocarditis[3]. In our study, patients of age older than 65 years constituted more than one quarter of the total patients diagnosed with IE. When compared to younger patients, there were more elderly patients experiencing hypertension, baseline serum creatinine levels greater than 2 mg/dl or end stage renal disease, and IE by *Staphylococcus aureus*, with fewer of them undergoing surgery during the same admission; all of which had been found to be associated with an increase in mortality in IE in previous studies[3]. We did not discover any factors other than age to be associated with mortality. Nevertheless, we confirmed that IE in elderly patients is a severe clinical condition, with an in-hospital mortality rate being as high as 54.2% (13 of 24 patients older than 65 years of age), which will be of special concern in an aging population such as we are experiencing here in Taiwan.

In a prospective, multinational cohort involving 1,552 patients diagnosed with native valve endocarditis, early surgery: defined as the replacement or repair of the affected valves during the initial hospitalization, was associated with a significant reduction in mortality[17]. A recent meta-analysis also found early surgery to be associated with a lower risk of mortality in patients with IE[18]. In our study, the in-hospital mortality rate in patients undergoing surgery during the same admission was 10.2% (five of 49 patients). However, our study did not find surgery during the same admission to be independently associated with a decrease in in-hospital mortality. This could possibly be better explained by the younger age of the patients who underwent surgery in our study.

In patients experiencing IE, systemic embolism occurs in 22 to 50% of them, and is frequently accompanied by devastating clinical outcomes[19]. In our study, more than 80% of embolic events occurred either prior to diagnosis or within one week after the diagnosis of IE, while more than 90% of embolic events occurred either prior to diagnosis or within two weeks after the diagnosis of IE. Our findings were compatible with the previous finding which showed that the embolic risk of IE falls dramatically after the first one to two weeks[20-22]. Whether or not surgery within this time frame could effectively

reduce the embolic risks is beyond the scope of our study, and thus requires further investigation.

Our study was limited by its retrospective design and small population. The analysis, which was taken from a single tertiary-care medical center, may have resulted in a selection bias towards more severe or complicated cases. Nevertheless, to our knowledge, this is the first study which has evaluated the clinical features, along with the risks associated with in-hospital mortality due to IE, in Taiwan after the year 2010. Despite diagnostic and therapeutic advances, mortality rate remain high in IE patients, particularly in the elderly. A well-versed understanding of contemporary microbiology guides clinicians to opt for the proper antibiotic regimen, although antibiotic resistance has emerged as an ongoing problem. Clinicians should not underestimate the prevalence of MRSA infection in patients with infective endocarditis.

Conflicts of interest statement

The authors declare there are no conflicts of interest regarding the publication of this article.

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感染性心內膜炎的臨床特徵與影響住院死亡率的因素—一家中台灣醫學中心從2012年到2016年的回溯性分析

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摘 要

本研究目的在於分析感染性心內膜炎患者的臨床特徵並探討影響住院死亡率的因素。本研究針對2012年1月至2016年12月的成人感染性心內膜炎患者進行回溯性分析。在87位納入研究對象的患者當中，57位(65.5%)為男性，30位(34.5%)為女性，平均年齡為54.1±16.6歲(範圍從18歲到85歲)。87位研究對象中有50位(57.5%)患者的二尖瓣受影響。32位(36.8%)患者有金黃色葡萄球菌菌血症，而14位(16.1%)患者有耐甲氧西林金黃色葡萄球菌菌血症。肝硬化(OR 18.38, 95% CI 2.46-137.20, p=0.007)與糖尿病(OR 4.52, 95% CI 1.01-20.30, p=0.049)與耐甲氧西林金黃色葡萄球菌菌血症有關。整體住院死亡率為23.0%。年齡大於65歲與較高的住院死亡率有關(OR of 5.81, 95% CI 1.62-20.87, p=0.007)。本研究發現感染性心內膜炎仍屬於致命性的疾病，尤其在老年人更是如此。臨床醫師勿低估耐甲氧西林金黃色葡萄球菌感染在感染性心內膜炎的盛行率。