Clinical and Echocardiographic Predictors of the In-Hospital Mortality and the Association with the Microorganisms in Patients with Infective Endocarditis

Achiraya Osateerakul, MD[1], Nithima Ratanasit, MD[2,3]

[1] Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [2] Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3] Her Majesty Cardiac Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Infective endocarditis (IE) is an infrequent, but serious disease with high mortality.

Objective: To evaluate the factors predicting the in-hospital mortality in patients with IE and to determine the association between factors and microorganisms.

Materials and Methods: The medical records of adult patients diagnosed with IE by modified Duke's criteria at Siriraj Hospital, the largest tertiary referral center and medical school in Thailand, between December 2014 and April 2020 were retrospectively reviewed.

Results: One hundred thirty-nine patients with IE were included with an average age of 54.4±15.9 years and 62.6% were male. Native valve endocarditis (NVE) was diagnosed in 77.3%. The three most common pathogens were *Streptococcus* spp. at 50.4%, culture negative IE at 16.5%, and Staphylococcus aureus at 12.2%. *Streptococcus* spp. was the more common in NVE (p=0.017) and mitral valve IE (p=0.042). Heart failure and embolic stroke occurred in 43.9% and 12.2% of patients, respectively. Valve surgery was performed on 63 patients. Aortic, mitral, and multi-valve involvements of IE were reported in 53.3%, 49.6%, and 10.1%, respectively. Valvular complications were detected in 40.3%, which were perforation, pseudoaneurysm, and perivalvular abscess in 30.2%, 8.6%, and 7.9%, respectively. The in-hospital mortality rate was 19.4% and significantly higher in older age (adjusted odd ratio [aOR] 1.05, 95% confidence interval [CI] 1.003 to 1.11), renal insufficiency (aOR 21.37, 95% CI 3.95 to 115.57) and higher pulmonary artery systolic pressure (aOR 1.008, 95% CI 1.03 to 1.13).

Conclusion: IE remains a serious disease with high mortality. The predictors of in-hospital mortality in patients with IE were age, renal insufficiency, and high pulmonary artery systolic pressure.

Keywords: Infective endocarditis; IE; In-hospital mortality; Predictor

Infective endocarditis (IE), an infection of endocardium is an uncommon, but serious disease. The clinical presentation can be fever, heart murmurs, embolic phenomena, and/or heart failure. Vegetations may lead to a variety of dreadful complications, such as valvular incompetence or obstruction, perforation, pseudoaneurysm, and perivalvular abscess. The diagnosis of IE may be challenging, and the mortality rate remains high with 14% to 22% in-hospital mortality rates[1]. Damlin et al. reported the in-hospital mortality rate among patients with IE of 7%[2]. Aortic, mitral, tricuspid, and pulmonic valve IE were reported in 39%, 40%, 22%, and 2%, respectively. Regarding the causative microorganisms of IE, it has changed over time. Historically, streptococcal species, especially from oral cavity flora, have been the prevalent bacterial pathogen. Nowadays, staphylococcal species represent a sizable proportion of IE cases. Furthermore, patients with advanced age, renal failure, and prosthetic valves are the majority of patients. The aims of the study were to evaluate the predictors of the in-hospital mortality in patients hospitalized for IE and the factors associated with microorganisms.

Materials and Methods

The present study was a retrospective cohort

Correspondence to:

Ratanasit N.

Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: +66-2-4196104, **Fax:** +66-2-4127412
Email: nithima.cha@mahidol.ac.th

Table 1. Baseline characteristics of patients with infective endocarditis and the comparison between dead and alive patients

	All (n=139)	Dead (n=25)	Alive (n=114)	p-value
Age (years); mean±SD	54.4±15.9	59.4±15.1	53.4±16.0	0.084
Female sex; n (%)	52 (37.4)	12 (48.0)	40 (35.1)	0.227
Native valve endocarditis; n (%)	108 (77.7)	20 (80.0)	88 (77.2)	0.760
Hypertension; n (%)	64 (46.0)	18 (72.0)	46 (40.4)	0.004
Previous infective endocarditis; n (%)	13 (9.4)	3 (12.0)	10 (8.8)	0.703
Previous valvular disease; n (%)	52 (37.4)	13 (52.0)	39 (34.2)	0.096
Atrial fibrillation; n (%)	16 (11.5)	6 (24.0)	10 (8.8)	0.042
Renal insufficiency; n (%)	21 (15.1)	11 (44.0)	10 (8.8)	<0.001
eGFR (mL/min/1.73 m²); median (IQR)	74.9 (28.7, 96.8)	25.3 (8.1, 77.4)	82.1 (47.2, 98.8)	0.001
Albumin (g/dL); median (IQR)	3.1 (2.8, 3.5)	2.9 (2.4, 3.2)	3.2 (2.9, 3.5)	0.008

eGFR=estimated glomerular filtration rate; IQR=interquartile range; SD=standard deviation

study in adult patients with the diagnosis of IE by modified Duke's criteria admitted between December 2014 and April 2020 at Siriraj Hospital, the largest tertiary referral center and medical school in Thailand. The medical records were retrospectively reviewed. The diagnosis of IE was identified from the computer record using ICD-10 I33.0 as the diagnostic code. The exclusion criteria were nosocomial IE, defined as IE diagnosed after 48 hours of admission, and patients with incomplete data. The clinical characteristics, basic blood chemistry, microbiological profile, valvular complications, heart failure, embolic phenomenon, echocardiographic findings, and outcomes were collected from the medical records, recorded, and statistically analyzed. The types of IE were classified as native valve IE (NVE) and prosthetic valve IE (PVE). Renal insufficiency was defined as the estimated glomerular filtration rate on admission of less than 15 mL/minute/1.73 m². The primary outcome was the in-hospital mortality. The present study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (037/2564).

Statistical analysis

Data analyses were performed, using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient demographics and baseline characteristics. Categorical variables were reported as frequency and percentage. Quantitative variables were reported as mean ± standard deviation in the normal distribution, and median or interquartile range in the skewed distribution. To evaluate factors that are associated with in-hospital mortality, the chi-square test or Fisher's exact test was performed, while the

quantitative factors employed the Independence sample t-test or Mann-Whitney U test. Variables with p-value less than 0.05 were further analyzed for independent association with mortality using multiple logistic regression. The results were reported as adjusted odds ratio (aOR) and 95% confidence interval (CI). A p-value of less than 0.05 was considered statistically significant.

Results

One hundred thirty-nine patients, aged 54.4±15.9 years with 62.6% male, enrolled in the present study. The mean hospital stay was 29 days. The three most common pathogens were *Streptococcus* spp. at 50.4%, culture negative IE at 16.5%, and *Staphylococcus aureus* (*S. aureus*) at 12.2%. No fungal IE was reported. *Streptococcus* spp. was significantly more common in NVE (p=0.017) and mitral valve IE (p=0.042). Baseline characteristics and causative pathogens of the present study population and those with and without the in-hospital mortality are shown in Table 1 and 2, respectively.

The echocardiographic findings showed that mean left ventricular ejection fraction in dead and alive groups were 60.0±14.8% and 63.6±12.8%, respectively (p=0.227). There was no statistically significant difference between the two groups regarding left atrial volume index, mean pulmonary artery pressure, and tricuspid annular plane systolic excursion. The most common complication was heart failure at 43.9%, followed by embolic stroke at 12.2%. Emergent or urgent valve surgery was performed in 63 patients or 45.3%. Aortic, mitral, and multi-valve involvement of IE were reported in 53.3%, 49.6%, and 10.1%, respectively. The mean vegetation size was 11.2 mm. Valvular complications were detected in 40.3%, which were perforation,

Table 2. Causative pathogens of infective endocarditis in all patients and the comparison between those in dead and alive patients

	All (n=139); n (%)	Dead (n=25); n (%)	Alive (n=114); n (%)	p-value
Streptococcus spp.	70 (50.4)	9 (36.0)	61 (53.5)	0.127
No organism identified	23 (16.5)	2 (8.0)	21 (18.4)	0.250
Staphylococcus aureus	17 (12.2)	4 (16.0)	13 (11.4)	0.509
Enterococcus spp.	12 (8.6)	6 (24.0)	6 (5.3)	0.008
Coagulase-negative staphylococci	10 (7.2)	3 (12.0)	7 (6.1)	0.386
Gram negative organisms	6 (4.3)	0 (0.0)	6 (5.3)	0.591
Other gram positive organism	1 (0.7)	1 (4.0)	0 (0.0)	0.180

Table 3. The echocardiographic findings in patients with infective endocarditis and the comparison between dead and alive patients

	All (n=139)	Dead (n=25)	Alive (n=114)	p-value
LVEF (%); mean±SD	62.9±13.2	60.0±14.8	63.6±12.8	0.227
LA volume index (mL/m²); median (IQR)	48.8 (36.8, 65.5)	55.2 (42.7, 75.4)	47.8 (36.4, 64.1)	0.142
RVSP (mmHg); mean±SD	50.8±18.1	60.1±22.2	49.0±16.7	0.024
mPAP (mmHg); mean±SD	32.5±10.1	35.5±12.4	31.8±9.5	0.192
TAPSE (mm); mean±SD	21.0±5.5	18.1±5.5	21.6±5.3	0.011
Number of vegetation; n (%)				0.505
No	32 (23.0)	6 (24.0)	26 (22.8)	
Single	79 (56.8)	12 (48.0)	67 (58.8)	
Multiple	28 (20.1)	7 (28.0)	21 (18.4)	
Mitral valve IE; n (%)	68 (49.6)	12 (50.0)	56 (49.6)	1.000
Aortic valve IE; n (%)	73 (53.3)	12 (50.0)	61 (54.0)	0.722
Multi-valve involvement; n (%)	14 (10.1)	4 (16.0)	10 (8.8)	0.201

IE=infective endocarditis; IQR=interquartile range; LA=left atrium; LVEF=left ventricular ejection fraction; mPAP=mean pulmonary artery pressure; RVSP=right ventricular systolic pressure; SD=standard deviation; TAPSE=tricuspid annular plane systolic excursion

Table 4. The in-hospital adverse outcomes of patients with infective endocarditis and the comparison between dead and alive patients

	All (n=139); n (%)	Dead (n=25); n (%)	Alive (n=114); n (%)	p-value
Heart failure	61 (43.9)	16 (64.0)	45 (39.5)	0.025
Embolic stroke	17 (12.2)	3 (12.0)	14 (12.3)	1.000
Valvular complications	56 (40.3)	14 (56.0)	42 (36.8)	0.077
Perforation	42 (30.2)	9 (36.0)	33 (28.9)	0.487
Pseudoaneurysm	12 (8.6)	4 (16.0)	8 (7.0)	0.228
Perivalvular abscess	11 (7.9)	2 (8.0)	9 (7.9)	1.000
Surgery	63 (45.3)	8 (32.0)	55 (48.2)	0.139

pseudoaneurysm, and perivalvular abscess in 30.2%, 8.6%, and 7.9%, respectively. Table 3 and 4 show the echocardiographic findings and outcomes, respectively.

The proportion of the cause of death was almost equal between non-cardiac at 56% and cardiac causes at 44%. The in-hospital mortality rate was 19.4% and significantly higher in older age (aOR 1.05, 95% CI 1.003 to 1.11), renal insufficiency (aOR 21.37, 95% CI 3.95 to 115.57), and higher pulmonary artery systolic pressure (aOR 1.008, 95% CI 1.03 to 1.13). Table 5 shows the univariate and multivariate

analyses of the in-hospital mortality. The associations between clinical parameters and microorganisms are demonstrated in Table 6.

Discussion

The in-hospital mortality rate in the present study was 19.4%, which was slightly higher than those reported in the previous studies from Thailand[3,4]. However, previous studies from developing countries showed a mortality rate of IE that was high, ranging from 24% to 46%[5]. The present study revealed that the in-hospital mortality was significantly higher in

Table 5. Univariate and multivariate analyses of the in-hospital mortality

Factors	Univariate		Multivariate	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1.027 (0.996 to 1.058)	0.087	1.054 (1.003 to 1.107)	0.037
Female gender	1.708 (0.713 to 4.092)	0.230		
Hypertension	3.801 (1.470 to 9.827)	0.006		
Renal insufficiency	8.171 (2.940 to 22.709)	<0.001	21.367 (3.951 to 115.572)	<0.001
Atrial fibrillation	3.284 (1.067 to 10.107)	0.038		
Albumin	0.282 (0.113 to 0.704)	0.007		
Enterococcus spp.	5.684 (1.658 to 19.489)	0.006		
RVSP	1.032 (1.003 to 1.063)	0.030	1.078 (1.028 to 1.130)	0.002
Heart failure	2.726 (1.110 to 6.697)	0.029		
Valvular complications	2.182 (0.908 to 5.242)	0.081		

CI=confidence interval; OR=odds ratio; RVSP=right ventricular systolic pressure

Table 6. The association between clinical parameters and microorganisms

	All (n=97)	*Staphylococcus* spp. (n=27)	*Streptococcus* spp. (n=70)	p-value
Native valve IE; n (%)	80 (82.5)	18 (66.7)	62 (88.6)	0.017
Age (years); mean±SD	54.9±15.2	53.7±13.1	55.3±16.0	0.628
Multiple vegetations; n (%)	22 (28.6)	7 (35.0)	15 (26.3)	0.460
Mitral valve IE; n (%)	52 (53.6)	10 (37.0)	42 (60.0)	0.042
Aortic valve IE; n (%)	45 (46.4)	15 (55.6)	30 (42.9)	0.261
Tricuspid valve IE; n (%)	4 (4.1)	3 (11.1)	1 (1.4)	0.064
Pulmonic valve IE; n (%)	4 (4.1)	0 (0.0)	4 (5.7)	0.573
Multi-valvular involvement; n (%)	9 (9.3)	2 (7.4)	7 (10.0)	0.708
Valvular complications; n (%)	36 (37.1)	12 (44.4)	24 (34.3)	0.353

IE=infective endocarditis; SD=standard deviation

the elderly, patients with renal insufficiency, and/or high pulmonary artery systolic pressure. Similarly, the mortality rate increased progressively with age, up from 50 years[6]. Aging is associated with higher prevalence of predisposing degenerative valve diseases and multiple comorbidities and increases the risk of death associated with IE. A prospective observational cohort study from Spain involving patients with NVE found the female gender was a predictor of death in the univariate analysis but not in the multivariate analysis[7]. The result from the present study showed no association between gender and the in-hospital mortality.

Prior study demonstrated that the type of pathogen and mortality were related, including the higher mortality in *S. aureus* IE[8,9]. However, *S. aureus* was always the most common pathogen in these studies. In contrast, the most common pathogens in the present study were Streptococci, followed by culture-negative IE. *S. aureus* is not independently associated with increased mortality, while Enterococci is associated with higher mortality

with a 5.7-fold risk in the univariate analysis, but the association was insignificant in the multivariate analysis. However, the explanation may be that Enterococci infection increased in prevalence in the elderly with multiple comorbidities.

In addition, previous studies revealed that renal insufficiency was the strong predictor of mortality[10,11]. The results of the present study demonstrated that the mortality among patients with IE is significantly higher in patients with renal insufficiency. The explanations might be related to the pathogen as the greater severity of IE due to *S. aureus*[12] and tubular toxicity caused by mitochondrial damage[13]. Tokarski et al. found that acute kidney injury was common in IE and most often associated with non-modifiable factors, including *S. aureus* infection[14].

Heart failure has been found to be a marker for increased mortality in most studies[8]. However, neither heart failure nor valvular complications show the statistical significance in the mortality rate in the present study. An explanation is that heart failure

at admission, when due to treatable disorders such as arrhythmia, fluid overload, may be controlled by medical treatment and the patients receive the standard treatment from specialist in the tertiary-care hospital.

Regarding the echocardiographic predictor of adverse events in patients with IE, vegetation size of more than 10 mm had been reported to predict the higher risk of embolization. However, the echocardiographic characteristics of vegetations were not the predictor of mortality[8]. In the present study, the mean vegetation size was 11.2 mm with no association with the in-hospital mortality. In addition, the authors investigated the echocardiographic parameters, including the numbers of vegetation and affected valve, valve location, left ventricular ejection fraction, left atrial volume index, pulmonary artery pressure, and tricuspid annular plane systolic excursion. The results showed that only high pulmonary artery systolic pressure is associated with the in-hospital mortality.

Limitation

The present study has limitations. The diagnosis of IE was established based on the modified Duke's criteria and mentioned in the final ICD-10 diagnosis. The nature of retrospective study has its own limitations. It is also a single-center study in a large tertiary referral center and medical school. Patients with nosocomial IE were excluded from the study due to the different patient setting. The external validation of the study results in a different population was not performed. Therefore, the findings may have referral biases and may not be applied to the general population.

Conclusion

IE is a serious disease with an increased cumulative incidence and mortality rate. To know the factors associated with mortality is important. From the present study, the predictors of the in-hospital mortality in patients with IE were age, renal insufficiency, and high pulmonary artery systolic pressure.

What is already known on this topic?

IE remains a serious cardiac disease with high overall mortality.

What does this study add?

Age, renal insufficiency, and high pulmonary artery systolic pressure are prognostic factors of poor outcome.

Conflicts of interest

The authors have no conflict of interest.

References

1. Sy RW, Kritharides L. Health care exposure and age in infective endocarditis: results of a contemporary population-based profile of 1536 patients in Australia. Eur Heart J 2010;31:1890-7.
2. Damlin A, Westling K, Maret E, Stålsby Lundborg C, Caidahl K, Eriksson MJ. Associations between echocardiographic manifestations and bacterial species in patients with infective endocarditis: a cohort study. BMC Infect Dis 2019;19:1052.
3. Reid KA, Barlasm RS, Mamas MA, Clark AB, Kwok CS, Wong CW, et al. Infective endocarditis is associated with worse outcomes in stroke: A Thailand National Database Study. Int J Clin Pract 2020;74:e13614.
4. Shakya S, Hussain S, Gordon S, Pettersson G, Shrestha N. Clinical presentation of infective endocarditis in the early 21st century: A descriptive study. Open Forum Infect Dis 2017;4:S559.
5. Cresti A, Chiavarelli M, Scalese M, Nencioni C, Valentini S, Guerrini F, et al. Epidemiological and mortality trends in infective endocarditis, a 17-year population-based prospective study. Cardiovasc Diagn Ther 2017;7:27-35.
6. Ahtela E, Oksi J, Sipilä J, Rautava P, Kytö V. Occurrence of fatal infective endocarditis: a population-based study in Finland. BMC Infect Dis 2019;19:987.
7. Sambola A, Fernández-Hidalgo N, Almirante B, Roca I, González-Alujas T, Serra B, et al. Sex differences in native-valve infective endocarditis in a single tertiary-care hospital. Am J Cardiol 2010;106:92-8.
8. Chu VH, Cabell CH, Benjamin DK Jr, Kuniholm EF, Fowler VG Jr, Engemann J, et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004;109:1745-9.
9. Gálvez-Acebal J, Rodríguez-Baño J, Martínez-Marcos FJ, Reguera JM, Plata A, Ruiz J, et al. Prognostic factors in left-sided endocarditis: results from the Andalusian multicenter cohort. BMC Infect Dis 2010;10:17.
10. Liau SK, Kuo G, Chen CY, Chen YC, Lu YA, Lin YJ, et al. In-hospital and long-term outcomes of infective endocarditis in chronic dialysis patients. Int J Gen Med 2021;14:425-34.
11. Spies C, Madison JR, Schatz IJ. Infective endocarditis

in patients with end-stage renal disease: clinical presentation and outcome. Arch Intern Med 2004;164:71-5.

12. Selton-Suty C, Célard M, Le Moing V, Doco-Lecompte T, Chirouze C, Iung B, et al. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clin Infect Dis 2012;54:1230-9.

13. Bartz RR, Fu P, Suliman HB, Crowley SD, MacGarvey NC, Welty-Wolf K, et al. Staphylococcus aureus sepsis induces early renal mitochondrial DNA repair and mitochondrial biogenesis in mice. PLoS One 2014;9:e100912.

14. Von Tokarski F, Lemaignen A, Portais A, Fauchier L, Hennekinne F, Sautenet B, et al. Risk factors and outcomes of early acute kidney injury in infective endocarditis: A retrospective cohort study. Int J Infect Dis 2020;99:421-7.