Factors associated with in-hospital mortality among infective endocarditis patients

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ABSTRACT

Introduction: Despite recent advancements in the diagnosis and management of infective endocarditis (IE), it is associated with substantial morbidity and mortality. Our study objective is to determine the factors associated with in-hospital mortality in IE patients among the local population.

Materials and Methods: All IE patients who were diagnosed with definite or possible IE and were treated at Sarawak Heart Centre from 1st January 2020 to 31st December 2022 were recruited. We examined the demographic features of the subjects and the factors that contributed to in-hospital mortality. Multivariate logistic regression was used to analyse the associated factors and in-hospital mortality.

Results: Our study population comprised a total of 37 patients with a mean age of 46.4 years and male predominance. The in-hospital mortality rate of IE in this study was 44.4%. Haemodynamic instability and anaemia were found to be strong predictors of IE survival outcome, with an odds ratio of 51.5 and 35.7 respectively. Patients with vascular phenomenon and heart failure were at 10.5- and 6.0-times higher odds of dying, however, these two associations were found to be not statistically significant.

Conclusion: The in-hospital mortality due to IE in our study was among the highest in developing countries. Factors of hypotension and optimal response to individual hemodynamic parameters may confer lower mortality. While anaemia is demonstrable as a risk factor for inpatient mortality, a target has yet to be reasonably established.

KEYWORDS:
Associated factors, infective endocarditis, in-hospital mortality

INTRODUCTION

There has been significant progress and improvements in the diagnosis as well as medical and surgical management of infective endocarditis (IE) in the last decade. Yet, it could result in fatal outcomes and is also characterised by substantial morbidity and mortality.[1,2] A systematic review involving 19 studies in developing countries showed mortality rates ranging from 7-46%.[3] Another study in Malaysia conducted by Sunil et al., reported a high in-hospital mortality rate of 35.7% and a complication rate as high as 85.7%.[4] Nevertheless, there is a dearth of research on IE in low- and middle-income (LMIC) countries.[3]

In developing countries, IE is a disease of male predominance.[5,6] Predisposing factors of IE and factors associated with mortality among IE patients are important in the management and prevention of IE. Many factors were found to increase predisposition to IE, which includes rheumatic heart disease, congenital heart disease, valvulopathy or previous valve replacement, and immunosuppressive state.[3,7-9] In addition, predictors of mortality in IE have been explored in previous research. A study done by Collonnaz et al., showed that prognostic factors of 3-month mortality include age ≥70 years, Charlson comorbidity index ≥2, Staphylococcal IE, septic shock, cerebral embolism, and serum creatinine level ≥18µmol/l; while prognostic factors of 1-year mortality include age ≥70 years, Charlson comorbidity index ≥2*time, high blood pressure*time, Staphylococcal IE, septic shock, cerebral embolism, and serum creatinine level ≥180µmol/l.[10] Among intravenous drug users who presented with a first episode of IE, surgery and referral to addiction treatment were associated with lower mortality while left-sided infection and bilateral involvement were associated with higher mortality.[11]

The primary objective of our study is to determine the factors associated with in-hospital mortality in IE patients among the local population. Hopefully, this will allow more focus on the delivery of care for these at-risk groups to improve the treatment outcome.

MATERIALS AND METHODS

Study Design and Setting

A descriptive study was conducted at the Department of Cardiology in the Sarawak Heart Centre (SHC), which is a tertiary cardiac centre located in an urban setting. This study design was selected to describe the factors that were associated with in-hospital mortality.

Participants

Participants consisted of patients who were diagnosed with IE and were treated at the Department of Cardiology, SHC from 1st January 2020 to 31st December 2022. Included were patients who were diagnosed with definite or possible IE using the Modified Duke's Criteria.[7] Excluded were patients

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who were initially diagnosed and treated as IE but were later confirmed to be other diagnoses.

Outcomes Measured
The primary outcome of this study was in-hospital mortality. In-hospital mortality was determined from patients' documented status upon discharge from the medical record.

Instruments Used
A baseline demographic form was used to collect the participants' baseline demographic data and other relevant information.

Data Collection
Demographic data such as patients' age, gender, ethnicity, and IE risk factors were collected in a retrospective manner. In addition, we also collected data on drug allergy, recent antibiotic use, presenting symptoms, vascular phenomenon, immunologic phenomenon, creatinine clearance, type of microorganisms cultured and complications that arose during the treatment. Information related to treatment adherence to the Malaysia Clinical Practice Guidelines (CPG) for the Prevention, Diagnosis and Management of Infective Endocarditis' such as blood culture collection process, echocardiographic features, and appropriateness of antibiotics and surgery, were gathered.

Data Analysis
Data were analysed using the Statistical Package for Social Science (SPSS) version 27.0 software (Chicago, Illinois, USA). Normality was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were used to describe the demographic data of participants. Categorical variables were presented using percentages and frequencies, whilst continuous variables were presented using the mean and standard deviation or median and interquartile ranges, depending on the normality. Parametric tests were used for data which were normally distributed whereas non-parametric tests were used for data which were not normally distributed. Multivariate logistic regression was then used to analyse the associated factors and in-hospital mortality. Statistical significance was set at p-value <0.05.

Ethics
Approval from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia was obtained before the commencement of the study (Approval number: NMRR ID-23-01673-6JT). Written informed consent was waived by the MREC.

RESULTS

Participant Recruitment
A total of 37 patients were recruited in the study. Initially, a total of 46 patients were selected using convenience sampling but nine patients were excluded, four were due to revision of diagnosis and the remaining five were due to the non-retrievable medical records.

Participant Profile
Table I showed the socio-demographic and clinical characteristics of the 37 patients in the study.

Primary Outcome
Seven out of the 42 factors in our study were shown to be associated with in-hospital mortality using Pearson's Chi-square test (Table II). These include anaemia (p=0.024), vascular phenomenon (p=0.020), classification of IE (p=0.023), complications (p=0.016), haemodynamic instability (p=0.001), heart failure (p=0.023), and embolic stroke (p=0.049). Those factors that were found to be statistically significant were further examined using multivariate logistic regression (Table III). As hemodynamic instability, heart failure and embolic stroke were complications of IE, only these variables were included in the multivariate analysis.

In the multivariate analysis, hemodynamic instability, anaemia, vascular phenomenon and heart failure were associated with in-hospital mortality, with odds ratios (95% confidence intervals, 95%CI) of 51.5 (95%CI 3.1, 853.3), 35.7 (95%CI 1.1, 1203.1), 10.5 (95%CI 0.7, 168.5) and 6.0 (95%CI 0.2, 147.6) respectively. However, vascular phenomenon and heart failure were not statistically significant.

DISCUSSION

Key Findings and Comparison to the Existing Literature
The mean age of the patients in our study was comparable to that of a Malaysian study performed from 2005 to 2017 (46.4 years vs. 50.0 years, respectively),[4] with male predominance. Among our study population, 13.5% had chronic rheumatic heart disease. This percentage is in tandem with the prevalence of rheumatic heart disease in our country of 14 per 1000 population.[12,13] Hence, appropriate prevention measures and management of rheumatic heart disease might play a role in the reduction of IE incidence.

About half of our study population had culture-negative IE, which was remarkably high as compared to only 22% in one Malaysian study.[4] This resulted in a lower proportion of definite IE among our study population. Negative cultures might be caused by a number of factors, including inappropriate blood culture-taking process, administration of antibiotics before blood culture collection, and recent antibiotic use. However, neither the negative culture nor the type of organisms cultured was significantly associated with in-hospital mortality in our study population.

Antibiotic therapy was considered appropriate if the correct antibiotic was used, using the correct route and for the correct duration.[14] Both the appropriateness of the empirical and culture-guided antibiotic therapy was remarkably low at 5.9% and 52.4% respectively, although both were not significantly associated with in-hospital mortality. Ceftriaxone was the most commonly prescribed antibiotic for empirical treatment among our patients, although it was not the recommended antibiotic according to our national guidelines.[7] It was a common antibiotic used due to its once-daily administration and avoidance of having to insert a central venous catheter. However, the usage of broad-spectrum antibiotics such as ceftriaxone for an extended duration may give rise to collateral damage, especially antibiotic resistance.[16,17]

Table I: Socio-demographic and clinical characteristics of the study population (n=37)

Characteristics	n (%)
Age (years)[a]	46.4 (17.0)
Gender	
Male	28 (75.7)
Female	9 (24.3)
Ethnicity	
Malay	9 (23.7)
Chinese	12 (31.6)
Indigenous	16 (42.1)
Presenting hospitals	
SHC	10 (27.0)
Others	27 (73.0)
Risk factors	
Pre-existing cardiopathy	3 (8.1)
Diabetes mellitus	6 (16.2)
Cancer	0 (0.0)
Chronic kidney disease	9 (24.3)
CRHD	5 (13.5)
non-CRHD valvulopathy	3 (8.1)
Valve prosthesis	5 (13.5)
CIED	1 (2.7)
Past history of IE	2 (5.4)
Intravenous drug user	2 (10.0)
Alcohol	4 (19.0)
Invasive procedure	2 (5.4)
Drug allergy	2 (5.7)
Recent antibiotic use	4 (10.5)
Signs and symptoms	
Fever	19 (52.8)
Weight loss	5 (13.9)
Appetite loss	8 (22.2)
Fatigue	11 (30.6)
Dyspnoea	15 (41.7)
Arthralgia	1 (2.8)
Vascular phenomenon	10 (27.0)
Immunologic phenomenon	1 (2.7)
Investigations	
Anaemia	23 (63.9)
ESR[a]	73 (25)
More than 20 mm/hour	33 (89.2)
CRP[b]	48 (222)
Creatinine clearance[b]	50.7 (32.0)
Had three sets of blood cultures obtained	26 (70.3)
Had echocardiogram performed	37 (100.0)
Culture-positive	21 (56.8)
Methicillin-sensitive *Staphylococcus aureus*	7 (33.3)
α-Streptococci	7 (33.3)
Enterococcus faecalis	2 (9.5)
Haemophilus *sp.*	1 (4.8)
Others	4 (19.0)
Echocardiogram	
Transthoracic	26 (70.3)
Transoesophageal	2 (5.4)
Both	9 (24.3)
Topography	
Aortic valve	10 (27.0)
Mitral valve	16 (43.2)
Aortic and mitral valves	4 (10.8)
Other valves	6 (16.2)
CIED	1 (2.7)
Vegetation size	
Longest diameterb	1.3 (1.2)
Less than 1 cm	8 (22.9)
1 cm or more	27 (77.1)

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Table I: Socio-demographic and clinical characteristics of the study population (n=37)

Characteristics	n (%)
Type of IE	
Native	32 (86.5)
Prosthetic, early	1 (2.7)
Prosthetic, late	2 (5.4)
CIED, early	1 (2.7)
CIED, late	0 (0.0)
Native and prosthetic	1 (2.7)
Classification of IE	
Definite	12 (32.4)
Possible	25 (67.6)
Empirical antibiotic	
Benzyl penicillin or ampicillin plus gentamicin	8 (21.6)
Ceftriaxone	25 (67.6)
Others	4 (10.8)
Appropriateness of antibiotic	
Empirical	2 (5.9)
Culture-guided	11 (52.4)
Surgery	
Indicated for surgery	35 (94.6)
Referral to cardiothoracic team for surgery	20 (60.6)
Surgery performed	0 (0.0)
Referral to infectious disease physician	10 (27.0)
Complications	31 (83.8)
Haemodynamic instability (Requiring ICU admission and/or intubation)	18 (48.6)
Severe valvular incompetence	20 (58.8)
Heart failure	15 (40.5)
Embolic stroke	9 (24.3)
Non-cerebral embolic localisation	6 (16.2)
Acute kidney injury	17 (45.9)
Transaminitis	8 (21.6)
Adverse drug reaction	2 (5.4)
In-hospital mortality outcome	
Alive	20 (55.6)
Dead	16 (44.4)
Alive	
With complication(s)	6 (30.0)
Without complication	14 (70.0)

CIED: Cardiac implantable electronic device, CRHD: Chronic rheumatic heart disease, CRP: C-Reactive protein, ESR: Erythrocyte sedimentation rate, ICU: Intensive care unit, IE: Infective endocarditis, SHC: Sarawak Heart Centre
[a]Presented in mean and standard deviation
[b]Presented in median and interquartile range

None of the patients in our cohort proceeded to cardiac surgery, with most having clinical indications for this.

The development of complications had a strong association with in-patient mortality, with haemodynamic instability being the most significant risk factor. The percentage of patients who developed complications in our study was comparable to the reported percentage in another study performed in Malaysia (83.8% vs.85.7% respectively).[4]

In our study, individuals who had anaemia at presentation were 35.7 times more likely to succumb to IE (p=0.046). This is an important finding as anaemia might reflect the severity of IE which is also an important prognostic indicator.[18]

The in-hospital mortality of our study population was greater than many of the developing countries (44.4% vs. 739% respectively), except for Brazil which has an IE in-hospital mortality rate of 46%.[3] This highlighted the dire need for greater efforts to improve IE management in order to reduce the seemingly higher mortality in our local setting. A significant portion of severely ill patients may be responsible for care escalation to a tertiary care facility in our cohort while relatively stable patients are typically retained in their respective peripheral hospitals, pooled statistical quantification of which remains challenging in heterogenous, resource-limited regions.

Strengths and Limitations

The limitations of this study were its single-centre design and small sample size. On the other hand, the strength of this study was that it represented the local population in Sarawak which has its unique geographical coverage and limitations, and little published data on this subject.

Recommendations

The primary determinants of oxygen supply are cardiac output, haemoglobin concentration and arterial blood oxygen saturation whereas blood pressure is the product of cardiac output and systemic vascular resistance.[19,20] Metric-based management of hypotension comprises four general steps: monitor perfusion, manage cause, maintain blood

Table II: Factors associated with in-hospital mortality (n=37)

Factors	Outcomesa		P-value
	Alive n (%)	Dead n (%)	
Age			
Age <50 years old	10 (55.6)	8 (44.4)	1.000
Age ≥50 years old	10 (55.6)	8 (44.4)	
Gender			
Male	14 (51.9)	13 (48.1)	0.439
Female	6 (66.7)	3 (33.3)	
Ethnics			
Malay	4 (50.0)	4 (50.0)	0.638
Chinese	8 (66.7)	4 (33.3)	
Indigenous	8 (50.0)	8 (50.0)	
Presenting hospital			
SHC	5 (50.0)	5 (50.0)	0.677
Others	15 (57.7)	11 (42.3)	
Cardiopathy			
Yes	2 (66.7)	1 (33.3)	0.686
No	18 (54.5)	15 (45.5)	
Diabetes mellitus			
Yes	3 (50.0)	3 (50.0)	0.764
No	17 (56.7)	13 (43.3)	
CKD			
Yes	3 (33.3)	6 (66.7)	0.121
No	17 (63.0)	10 (37.0)	
CRHD			
Yes	2 (40.0)	3 (60.0)	0.451
No	18 (58.1)	13 (41.9)	
non-CRHD valvulopathy			
Yes	2 (66.7)	1 (33.3)	0.686
No	18 (54.5)	15 (45.5)	
Valve prosthesis			
Yes	2 (40.0)	3 (60.0)	0.451
No	18 (58.1)	13 (41.9)	
CIED			
Yes	1 (100.0)	0 (0.0)	0.364
No	19 (54.3)	16 (45.7)	
Past history of IE			
Yes	0 (0.0)	2 (100.0)	0.340
No	20 (58.8)	14 (41.2)	
IVDU			
Yes	0 (0.0)	2 (100.0)	0.080
No	11 (64.7)	6 (35.3)	
Alcohol			
Yes	2 (50.0)	2 (50.0)	0.648
No	10 (62.5)	6 (37.5)	
Invasive procedure			
Yes	1 (50.0)	1 (50.0)	0.871
No	19 (55.9)	15 (44.1)	
Drug allergy			
Yes	2 (100.0)	0 (0.0)	0.169
No	16 (50.0)	16 (50.0)	
Fever			
Yes	13 (72.2)	5 (27.8)	0.064
No	7 (41.2)	10 (58.8)	
Weight loss			
Yes	3 (60.0)	2 (40.0)	0.889
No	17 (56.7)	13 (43.3)	
Appetite loss			
Yes	4 (57.1)	3 (42.9)	1.000
No	16 (57.1)	12 (42.9)	
Fatigue			
Yes	5 (45.5)	6 (54.5)	0.344
No	15 (62.5)	9 (37.5)	
Dyspnoea			
Yes	6 (40.0)	9 (60.0)	0.076
No	14 (70.0)	6 (30.0)	
Arthralgia			
Yes	0 (0.0)	1 (100.0)	0.241
No	20 (58.8)	14 (41.2)	

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Table II: Factors associated with in-hospital mortality (n=37)

Factors	Outcomesa		P-value
	Alive n (%)	Dead n (%)Anaemia	
Anaemia			
Yes	10 (43.5)	13 (56.5)	0.024
No	10 (83.3)	2 (16.7)	
ESR			
20 mm/hour or less	4 (100.0)	0 (0.0)	0.058
More than 20 mm/hour	16 (50.0)	16 (50.0)	
Vascular phenomenon			
Yes	2 (22.2)	7 (77.8)	0.020
No	18 (66.7)	9 (33.3)	
Immunologic phenomenon			
Yes	1 (100.0)	0 (0.0)	0.364
No	19 (54.3)	16 (45.7)	
Classification of IE			
Definite	3 (27.3)	8 (72.7)	0.028
Possible	17 (68.0)	8 (32.0)	
Vegetation size			
Less than 1cm	3 (37.5)	5 (62.5)	0.317
1 cm or more	15 (57.7)	11 (42.3)	
Culture-positive			
Yes	9 (45.0)	11 (55.0)	0.154
No	11 (68.8)	5 (31.3)	
Organism cultured			
Methicillin-sensitive Staphylococcus aureus	3 (42.9)	4 (57.1)	0.904
Streptococci	3 (42.9)	4 (57.1)	
Enterococci	1 (50.0)	1 (50.0)	
Others	2 (66.7)	1 (33.3)	
Choice of empirical antibiotic			
Benzyl penicillin or ampicillin plus gentamicin	4 (50.0)	4 (50.0)	0.353
Ceftriaxone	15 (62.5)	9 (37.5)	
Others	1 (25.0)	3 (75.0)	
Appropriateness of empirical antibiotic			
Yes	0 (0.0)	2 (100.0)	0.133
No	17 (54.8)	14 (45.2)	
Appropriateness of culture-guided antibiotic			
Yes	4 (40.0)	6 (60.0)	0.653
No	5 (50.0)	5 (50.0)	
Referral to cardiothoracic surgeon			
Yes	8 (42.1)	11 (57.9)	0.280
No	8 (61.5)	5 (38.5)	
Referral to infectious disease physician			
Yes	6 (60.0)	4 (40.0)	0.739
No	14 (53.8)	12 (46.2)	
Complications			
Yes	14 (46.7)	16 (53.3)	0.016
No	8 (100.0)	0 (0.0)	
Haemodynamic instability (Requiring ICU admission and/ or intubation)			
Yes	3 (17.6)	14 (82.4)	< 0.001
No	17 (89.5)	2 (10.5)	
Severe valvular incompetence			
Yes	8 (42.1)	11 (57.9)	0.208
No	9 (64.3)	5 (35.7)	
Heart failure			
Yes	5 (33.3)	10 (66.7)	0.023
No	15 (71.4)	6 (28.6)	
Stroke secondary to vegetation embolism			
Yes	2 (25.0)	6 (75.0)	0.049
No	18 (64.3)	10 (35.7)	
Non-cerebral embolic localisation			
Yes	2 (33.3)	4 (66.7)	0.230
No	18 (60.0)	12 (40.0)	
Acute kidney injury			
Yes	6 (37.5)	10 (62.5)	0.051
No	14 (70.0)	6 (30.0)	
Transaminitis			
Yes	3 (37.5)	5 (62.5)	0.244
No	17 (60.7)	11 (39.3)	

CIED: Cardiac implantable electronic device, CRHD: Chronic rheumatic heart disease, ICU: Intensive care unit, IE: Infective endocarditis, SHC: Sarawak Heart Centre

Table III: Multivariate analysis of in-hospital mortality among IE patients. (n=37)

Variables	Odds Ratio	95% CI	P-value
Anaemia			
Yes	35.7	1.1, 1203.1	0.046
No	Reference group		
Vascular phenomenon			
Yes	6.0	0.2, 147.6	0.274
No	Reference group		
Haemodynamic instability			
Yes	51.5	3.1, 853.3	0.006
No	Reference group		
Heart failure			
Yes	10.5	0.7, 168.5	0.097
No	Reference group		

IE: Infective endocarditis; 95%CI - 95% Confidence Intervals.

pressure and match supply to demand,[19] which may result in better mortality outcomes.

Restrictive transfusion has been proposed in non-bleeding anaemic, critically ill patients though a target has yet to be established and it does not necessarily confer a better outcome.[21-24] Consideration for transfusion on an ad hoc basis should be exercised with caution. Although utilising prospective trials may be considered an optimal approach, the presence of cohort heterogeneity and ethical considerations regarding possible adverse outcomes could pose challenges in terms of designing such studies.

With regard to national efforts in curbing the disease, an IE registry could be initiated for the consolidation of data on the disease nationwide and to identify key areas that could potentially improve the management of IE in our country. This plays an important part in the learning of the disease characteristics among our local population and to tailor the management according to the clinical requirement. The distribution of resources could also focus on key areas that have the most potential to improve IE mortality outcomes.

At the hospital level, interval clinical audits are imperial to ensure quality control and improvements, especially on the method of blood culture collection and the appropriateness of antibiotic treatments in accordance with our national guidelines. Clinical audits also enable healthcare personnel to keep constantly updated with the latest knowledge in IE management in order to deliver the best treatment to patients through regular continuing medical education (CME) at every hospital level as part of the audit cycle.

Human capital development, specifically those involved in the management of IE, should be accelerated, as are facilities required to manage IE, especially when there is multisystem involvement.

CONCLUSION

The in-hospital mortality due to IE in our study was among the highest in developing countries. Factors of hypotension and optimal response to individual hemodynamic parameters may confer lower mortality. While anaemia is demonstrable as a risk factor for inpatient mortality, a target has yet to be reasonably established.

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