

Clinical Characteristics and Risk Factors for in-Hospital Mortality in 240 Cases of Infective Endocarditis in a Tertiary Hospital in China: A Retrospective Study

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Purpose: This study aimed (i) to investigate the clinical characteristics and risk factors related to in-hospital mortality in patients with infective endocarditis (IE) and (ii) to compare the differences in three age groups.

Methods: A total of 240 IE cases diagnosed using the modified Duke criteria between January 2016 and December 2019 were included and retrospectively studied. Patients were stratified into three age groups: < 50 y, 50–65 y, and > 65 y.

Results: The mean age of the patients was 51 ± 14 y, and 154 patients (64.2%) were male. In addition, 136 (56.7%) patients with IE had no previous cardiac disease. Congenital heart disease (CHD, 21.3%) was the most common underlying heart disease, followed by rheumatic heart disease (RHD, 8.8%). *Streptococcus* was found in 55 (22.9%) patients and was the most common causative pathogen, comprising 52.9% of all positive blood cultures. Echocardiography showed the presence of vegetations in 88.3% of cases and the predominant involvement of the left heart valves. Fever and cardiac murmur were the most frequent presentations, with no significant differences among age groups. Compared with younger patients, elderly patients had a lower operation rate and higher in-hospital mortality. The independent risk factors of in-hospital mortality were age > 65 y, intracranial infection, splenic embolization, cerebral hemorrhage, NYHA class III–IV, and prosthetic valve infection.

Conclusion: CHD replaces RHD as the most common underlying heart disease in IE patients. Patients without previous cardiac disease are at increased risk of IE. *Streptococcus* is still the primary causative pathogen of IE. Elderly patients present with more comorbidities and complications, in addition to a more severe prognosis than younger patients. Age older than 65 y, intracranial infection, splenic embolization, cerebral hemorrhage, NYHA class III–IV, and prosthetic valve infection showed poorer in-hospital outcomes.

Keywords: infective endocarditis, clinical characteristics, risk factors, elderly patients

Introduction

Infective endocarditis (IE) is the infection of the heart valve, the endocardial surface, or the septum and accompanying systemic pathological process.¹ The overall morbidity of IE in developed countries ranges between 30 and 100 episodes per million individuals annually.² However, the incidence of IE in recent years has increased with the application of prosthetic valve replacement, indwelling cardiac devices, and various endovascular treatment technologies.³ IE is a life-threatening disease with high mortality rates of 14–22% in-hospital and reaching 51% at 10 years despite advances in medical and surgical care.⁴ The prognosis for patients with IE is strongly dependent on early diagnosis and prompt treatment. However, the clinical presentation of IE can be highly variable and nonspecific, which potentially leads to a significant delay in diagnosis, thus negatively affecting patient prognosis.⁵ The epidemiological characteristics of IE

have recently changed owing to the evolution of medical practice and demographic changes.⁶ Moreover, the incidence of IE in elderly patients has increased because of the aging general population and the increased proportion of comorbidities.^{4,7,8} Age is currently included as a predictor in several risk scores and is regarded as an important independent predictor of mortality in patients with IE.^{7,9,10}

Therefore, the objectives of this study are as follows: (1) to analyze the clinical features, echocardiogram, and microbiological profile of IE and compare the three age groups and (2) to explore the prognostic risk factors of in-hospital mortality.

Materials and Methods

Patients

This study was conducted at the First Affiliated Hospital of Nanjing Medical University, a tertiary general hospital with 4200 licensed beds in East China. Patients diagnosed with definite IE in accordance with the modified Duke criteria¹¹ between January 2016 and December 2019 were included (Figure 1). Incomplete case records, nonhospitalization, indefinite diagnosis, or untreated IE comprised the exclusion criteria for this study. Ultimately, 240 inpatients were enrolled.

Data Extraction and Study Design

Data were retrieved from electronic medical records. The collected data included the demographic information, clinical features, predisposing factors, pathogenic microorganisms in the blood, echocardiographic findings, complications, treatments, and prognoses (in-hospital and one-year mortality) of the patients. The patients were classified into three groups by age. For each age group, the number of patients was as follows: under 40 y, 104 (43.3%); 50–65 y, 103

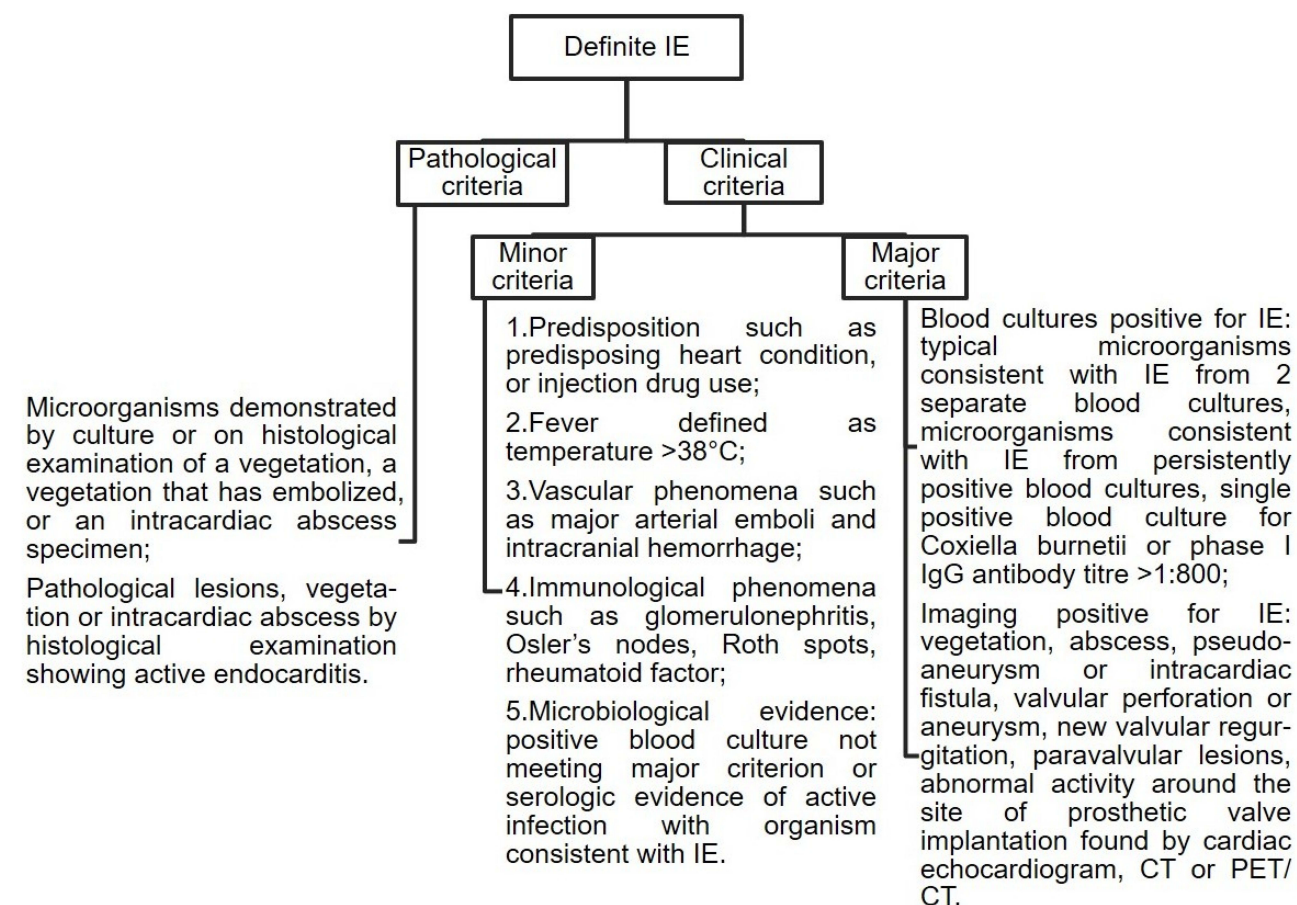


Figure 1 Definite diagnosis of IE according to the modified Duke criteria.

(42.9%); over 65 y, 33 (13.8%). To explore the risk factors of in-hospital mortality, we subdivided the patients into the survival group and the death group.

Definition

For a definitive diagnosis of IE, the ESC guidelines for pathological and clinical criteria were used as reference. Although some patients with negative blood cultures failed to meet the clinical criteria, IE patients confirmed by intraoperative exploration and postoperative pathology were included in this study. A total of 192 patients were definitively diagnosed with IE on the basis of the following criteria: two major criteria or positive blood culture plus intraoperative exploration, or vegetations or valve lesions (found by echocardiography or during operation) plus positive pathology or valve/embolus culture. Meanwhile, 48 patients with definite IE met one major criterion plus three minor criteria.

Congenital heart disease (CHD) was coded using Q20 to Q28, and rheumatic heart disease (RHD) was coded using I05 to I09 in the International Classification of Diseases, Tenth Revision (ICD-10).

Complications of IE were defined as follows: septic shock (the presence of an acute circulatory failure in sepsis, characterized by persistent arterial hypotension—ie, systolic pressure < 90 mmHg despite adequate volume resuscitation); embolic events, including intracranial complications (eg, hemorrhage and infarction) and peripheral embolic events mainly characterized by splenomegaly or splenic embolism; functional class III–IV in accordance with the New York Heart Association (NYHA) classification; atrial fibrillation (a common arrhythmia in patients with acute conditions attributed to inflammation and hemodynamic change).^{6,12,13}

As the main diagnostic methods for IE, transthoracic echocardiogram and blood culture were conducted on all patients. However, PCR testing of valve culture was not performed, similar to *anti-Legionella*, *Bartonella*, *Coxiella burnetii*, and *Mycoplasma* antibody tests. Indications for cardiac surgery were based on the 2015 ESC guidelines for the management of IE patients with heart failure, uncontrolled infections, embolic events, and vegetation size > 10 mm were required to undergo early surgical intervention. The time until surgery was defined as the interval between the diagnosis of IE and the date of surgery.¹⁴

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, United States). The data were presented as mean \pm standard deviation and median for continuous variables and as frequencies and percentages for categorical variables. Comparison of baseline characteristics between groups (A: under 50 y, B: 50–65 y, and C: > 65 y) was performed using the chi-square test. In-hospital mortality was defined as death from any cause during hospitalization. Univariate analysis was performed using the chi-square or Fisher's exact tests as appropriate for categorical variables. After univariate analysis, variables with $P < 0.05$ were included in multivariate analysis to identify predictors for in-hospital mortality among IE patients. Odds ratios (OR) with a 95% confidence interval (CI) were calculated in logistic regression. P -value < 0.05 was considered statistically significant.

Results

Clinical Characteristics of IE Patients

The clinical features, echocardiographic data, and causative microorganisms of 240 IE patients are summarized in Table 1. The mean age of patients was 51 ± 14 y, and 154 cases (64.2%) were male.

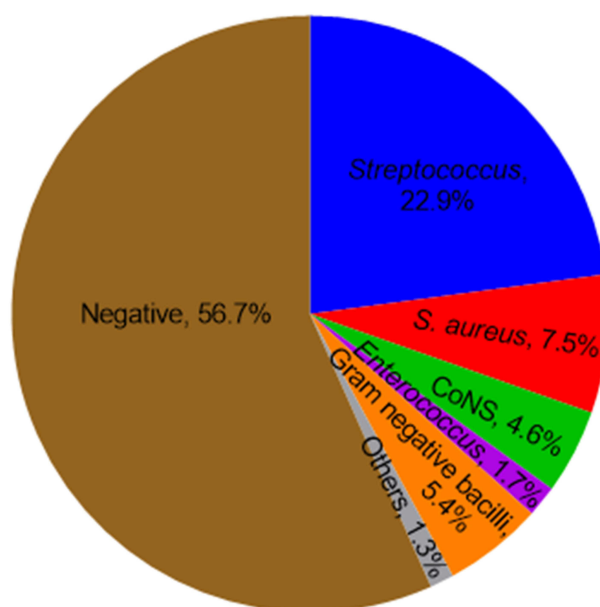
The most frequent clinical presentations were fever (78.8%) and chest tightness/asthma (43.3%). Cardiac murmur was found in 85.4% of patients during physical examination, and 136 (56.7%) patients with IE had no previous cardiac disease. Among the patients with underlying heart disease (43.3%), 51 (21.3%) patients had CHD—mainly bicuspid aortic valve (25 cases), ventricular septal defect (16 cases), and patent foramen ovale (6 cases). In addition, 21 (8.8%) cases had a history of RHD. The most prevalent comorbidities were hypertension (25.0%) and diabetes (12.5%). Cerebrovascular accident, splenomegaly, and decreased cardiac function were prominent complications observed in IE patients. Atrial fibrillation rhythm was observed in 22 patients during hospitalization.

Table 1 Clinical Features, Echocardiography and Microbiology of 240 IE Cases

Variables	n (%)	Variables	n (%)
Male	154 (64.2)	Echocardiographic data	
Clinical manifestations		Vegetation size ≥ 10 mm	116 (48.3)
Fever	189 (78.8)	Mitral location	124 (51.7)
Chest tightness/asthma	104 (43.3)	Aortic location	116 (48.3)
Cardiac murmur	205 (85.4)	Multivalvular infection	49 (20.4)
Predisposing factors		Prosthetic valves infection	21 (8.8)
CHD	51 (21.3)	Valvular perforation	37 (15.4)
RHD	21 (8.8)	Paravalvular abscess	28 (11.7)
Previous heart valve surgery	23 (9.6)	Moderate or severe valve stenosis	17 (7.1)
Comorbidities		Rupture of chordae tendinca	20 (8.3)
Hypertension	60 (25.0)	Complications	
Diabetes	30 (12.5)	Intracranial infection	14 (5.8)
Renal disease	8 (3.3)	Septic shock	6 (2.5)
Liver disease	7 (2.9)	Splenomegaly	48 (20.0)
History of cancer	11 (4.6)	Cerebral hemorrhage	18 (7.5)
Dialysis	5 (2.1)	Cerebral emboli	21 (8.8)
Intravenous drug use	2 (0.8)	Atrial fibrillation	22 (9.2)
Surgical treatment	173 (72.1)	NYHA class III–IV	90 (37.5)
In-hospital mortality	15 (6.3)	One-year mortality	19 (7.9)

Vegetations were detected in 212 (88.3%) patients by echocardiography. Native valve involvement was detected in 215 (89.6%) patients, followed by prosthetic valve-related IE (8.8%) and cardiac device-related IE (1.7%). The distribution of valve involvement was as follows: mitral valve (51.7%), aortic valve (48.3%), tricuspid valve (6.7%), pulmonary valve (3.3%), and multiple valves (20.4%). No vegetations were found by echocardiography in 11.7% (28/240) of patients; however, vegetations, valve lesions (such as valve perforation, perivalvular abscesses, or rupture of chordae tendineae), or pseudoaneurysms were found intraoperatively in 20 of the patients. Positive blood cultures were detected in 8 patients.

Blood cultures were positive in 104 (43.3%) patients, and 108 strains were isolated (Figure 2). *Streptococcus* was the most common microorganism, found in 55 (22.9%) patients and comprising 52.9% of all positive blood cultures. *S. aureus* and

**Figure 2** Results of blood culture in 240 IE patients.

coagulase-negative Staphylococcus (CoNS) constituted 7.5% and 4.6% of the microorganisms, respectively. *S. aureus* was detected by blood culture in 83.3% of patients with septic shock, 28.6% of whom had an intracranial infection. Meanwhile, 5 methicillin-resistant *S. aureus* (MRSA) and 6 methicillin-resistant CoNS (MRCNS) strains were isolated from blood culture by antimicrobial susceptibility testing. The resistance rates of *S. aureus* and CoNS to penicillin were 88.9% and 90.9%, respectively. No *Streptococcus* and *Staphylococcus* resistance to vancomycin and linezolid were isolated. In addition, 1 strain of *E. faecalis* exhibited resistance to linezolid, but no *Enterococcus* showed resistance to vancomycin. The gram-negative bacilli were composed of 4 strains of *Acinetobacter*, 4 strains of *Haemophilus*, 1 strain each of *Escherichia coli*, *Stenotrophomonas maltophilia*, *Brucella*, *Aggregatibacter actinomycetemcomitans*, and *Brevundimonas diminuta*.

Among the IE patients, 56.7% had negative blood culture, and 75.0% (102/136) had previous antibiotic therapy. Cardiac surgery was conducted on 72.1% (98/136) of the patients with negative blood cultures. Meanwhile, 60 patients underwent valve cultures, 16 of which were positive (including 10 strains of *Streptococcus*, 3 strains of CoNS, 2 strains of *S. aureus*, and 1 strain of *Pseudomonas schisterii*). Overall, the in-hospital mortality of the IE patients was 6.3%, of which 19 patients (7.9%) died during the one-year follow-up. The mean time between diagnosis and surgery was 14 ± 13 d (median=10 d).

Comparison Between Three Groups Classified by Age

The 240 IE patients were divided into three groups by age (listed in Table 2): 104 patients in Group A, 103 patients in Group B, and 33 patients in Group C. No statistically significant difference in the clinical presentations (fever and cardiac murmur) of IE was found between the age groups. Group A had a significantly higher percentage of cases with CHD (29.8%), splenomegaly (29.8%), multivalvular infection (26.9%), and paravalvular abscess (15.4%) than other age groups. Chest tightness/asthma symptoms (50.5%), diabetes comorbidity (18.4%), and vegetation size ≥ 10 mm (60.2%) more frequently occurred in Group B than in Group A. However, the frequencies of occurrence of hypertension (63.6%), atrial fibrillation (10.7%), and enterococcal bloodstream infection (9.1%) were significantly higher in Group C than in other groups. Previous heart valve surgery, renal or liver disease, prosthetic valve infection, septic shock, and gram-negative bacilli infection were more common in Group C than in other age groups; however, no statistical difference was indicated. The proportions of surgical treatment were 72.1% (Group A), 76.9% (Group B), and 51.5% (Group C), respectively. The in-hospital mortality of the IE patients in Group C (18.2%) was significantly higher than those in Groups A (4.9%) and B (3.9%).

Table 2 Characteristics of 240 Patients with IE in the Three Age Groups

Variables, n (%)	Group A (N=104)	Group B (N=103)	Group C (N=33)	P-value		
				A vs B	B vs C	A vs C
Male	66 (63.5)	69 (67.0)	19 (57.6)	0.594	0.325	0.544
Clinical manifestations						
Fever	82 (78.8)	79 (76.7)	28 (84.8)	0.710	0.320	0.450
Chest tightness/asthma	37 (35.6)	52 (50.5)	15 (45.5)	0.030*	0.615	0.308
Cardiac murmur	90 (86.5)	87 (84.5)	28 (84.8)	0.672	0.958	0.807
Predisposing factors						
CHD	31 (29.8)	18 (17.5)	2 (6.1)	0.037*	0.107	0.005*
RHD	6 (5.8)	12 (11.7)	3 (9.1)	0.133	0.683	0.502
Previous heart valve surgery	10 (9.6)	9 (8.7)	4 (12.1)	0.827	0.565	0.679
Comorbidities						
Hypertension	9 (8.7)	30 (29.1)	21 (63.6)	<0.001*	<0.001*	<0.001*
Diabetes	6 (5.8)	19 (18.4)	5 (15.2)	0.005*	0.666	0.084
Renal disease	2 (1.9)	3 (2.9)	3 (9.1)	0.643	0.133	0.056
Liver disease	4 (3.8)	1 (1.0)	2 (6.1)	0.178	0.083	0.588
History of cancer	3 (2.9)	4 (3.9)	4 (12.1)	0.691	0.080	0.036*
Dialysis	3 (2.9)	1 (1.0)	1 (3.0)	0.317	0.392	0.965

(Continued)

Table 2 (Continued).

Variables, n (%)	Group A (N=104)	Group B (N=103)	Group C (N=33)	P-value		
				A vs B	B vs C	A vs C
Complications						
Intracranial infection	8 (7.7)	5 (4.9)	1 (3.0)	0.400	0.657	0.346
Septic shock	2 (1.9)	2 (1.9)	2 (6.1)	0.992	0.223	0.219
Splenomegaly	31 (29.8)	14 (13.6)	3 (9.1)	0.005*	0.496	0.016*
Cerebral hemorrhage	8 (7.7)	9 (8.7)	1 (3.0)	0.784	0.274	0.346
Cerebral emboli	10 (9.6)	9 (8.7)	2 (6.1)	0.827	0.624	0.529
Atrial fibrillation	3 (2.9)	11 (10.7)	8 (24.2)	0.026*	0.050	<0.001*
NYHA class III–IV	38 (36.5)	38 (36.9)	14 (42.4)	0.958	0.569	0.544
Echocardiographic data						
Vegetation size ≥ 10mm	42 (40.4)	62 (60.2)	12 (36.4)	0.004*	0.017*	0.680
Mitral location	53 (51.0)	54 (52.4)	17 (51.5)	0.833	0.927	0.956
Aortic location	53 (51.0)	47 (45.6)	16 (48.5)	0.443	0.775	0.804
Multivalvular infection	28 (26.9)	14 (13.6)	7 (21.2)	0.017*	0.292	0.512
Prosthetic valves infection	9 (8.7)	9 (8.7)	3 (9.1)	0.983	0.950	0.938
Valvular perforation	15 (14.4)	17 (16.5)	5 (15.2)	0.679	0.854	0.918
Paravalvular abscess	16 (15.4)	12 (11.7)	0	0.432	0.040*	0.017*
Moderate or severe valve stenosis	4 (3.8)	11 (10.7)	2 (6.1)	0.058	0.432	0.588
Rupture of chordae tendinca	8 (7.7)	12 (11.7)	1 (3.0)	0.335	0.143	0.346
Causative microorganism						
<i>Streptococcus</i> spp.	28 (26.9)	23 (22.3)	4 (12.1)	0.443	0.201	0.080
<i>Staphylococcus aureus</i>	9 (8.7)	8 (7.8)	1 (3.0)	0.816	0.341	0.279
CoNS	5 (4.8)	4 (3.9)	2 (6.1)	0.744	0.596	0.776
<i>Enterococcus</i>	0	1 (1.0)	3 (9.1)	0.314	0.016*	0.002*
Gram-negative bacilli	6 (5.8)	3 (2.9)	3 (9.1)	0.314	0.133	0.502
Negative blood culture	57 (54.8)	63 (61.2)	16 (48.5)	0.354	0.199	0.526
Surgical treatment	80 (76.9)	76 (73.8)	17 (51.5)	0.601	0.017*	0.005*
In-hospital mortality	5 (4.9)	4 (3.9)	6 (18.2)	0.744	0.006*	0.014*

Note: *P<0.05.

Risk Factors for in-Hospital Mortality

The risk factors associated with in-hospital mortality were analyzed. The results are listed in Table 3. Univariate analysis showed that the following factors were associated with the in-hospital mortality: age over 65 y, CHD, previous heart valve surgery, intracranial infection, septic shock, splenic embolization, cerebral hemorrhage, atrial fibrillation, NYHA class III–IV, prosthetic valve infection, gram-negative bacilli infection, and surgical treatment.

Table 3 Risk Factors of In-Hospital Outcome in Patients with IE (Univariate Analysis)

Variables, n (%)	Survivors, N=225	Death, N=15	P-value
Age >65 y	27 (12.0)	6 (40.0)	0.002*
Male	143 (63.6)	11 (73.3)	0.444
Clinical manifestations			
Fever	117 (52.0)	12 (80.0)	0.903
Chest tightness/asthma	99 (44.0)	5 (33.3)	0.420
Cardiac murmur	193 (85.8)	12 (80.0)	0.539
Predisposing factors			
CHD	51 (22.7)	0	0.038*
RHD	19 (8.4)	2 (13.3)	0.516
Previous heart valve surgery	19 (8.4)	4 (26.7)	0.020*

(Continued)

Table 3 (Continued).

Variables, n (%)	Survivors, N=225	Death, N=15	P-value
Complications			
Intracranial infection	9 (4.0)	5 (33.3)	<0.001*
Septic shock	3 (1.3)	3 (20.0)	<0.001*
Splenic embolization	5 (2.2)	3 (20.0)	<0.001*
Cerebral hemorrhage	13 (5.8)	5 (33.3)	<0.001*
Cerebral emboli	19 (8.4)	2 (13.3)	0.516
Atrial fibrillation	18 (8.0)	4 (26.7)	0.015*
NYHA class III–IV	80 (35.6)	10 (66.7)	0.016*
Echocardiographic data			
Vegetation size ≥ 10mm	108 (48.0)	8 (53.3)	0.689
Mitral location	115 (51.1)	9 (60.0)	0.505
Aortic location	106 (47.1)	10 (66.7)	0.142
Multivalvular infection	45 (20.0)	4 (26.7)	0.535
Prosthetic valve infection	17 (7.6)	4 (26.7)	0.011*
Causative microorganism			
<i>Streptococcus spp.</i>	54 (24.0)	1 (6.7)	0.122
<i>S. aureus</i>	15 (6.7)	3 (20.0)	0.058
CoNS	10 (4.4)	1 (6.7)	0.690
<i>Enterococcus faecalis</i>	3 (1.3)	1 (6.7)	0.118
Gram-negative bacilli	9 (4.0)	3 (20.0)	0.006*
Surgical treatment	167 (74.2)	6 (40.0)	0.004*

Note: * $P < 0.05$.

Table 4 Risk Factors of In-Hospital Mortality in Patients with IE (Multivariate Analysis)

Variables	P-value	OR	95% CI
Age >65 y	0.005	13.357	2.220–80.345
Intracranial infection	0.004	19.397	2.586–145.500
Splenic embolization	0.015	26.493	1.906–368.186
Cerebral hemorrhage	0.008	12.851	1.959–84.326
NYHA class III–IV	0.016	7.636	1.471–39.644
Prosthetic valve infection	0.045	6.633	1.042–42.205

Multifactorial analysis was conducted on clinical variables that were determined as statistically significant by univariate analysis. The following were identified as independent predictors of in-hospital mortality (Table 4): age over 65 y ($P=0.005$, OR=13.357, 95% CI 2.220–80.345), intracranial infection ($P=0.004$, OR=19.397, 95% CI 2.586–145.500), splenic embolization ($P=0.015$, OR=26.493, 95% CI 1.906–368.186), cerebral hemorrhage ($P=0.008$, OR=12.851, 95% CI 1.959–84.326), NYHA class III–IV ($P=0.016$, OR=7.636, 95% CI 1.471–39.644), and prosthetic valve infection ($P=0.045$, OR=6.633, 95% CI 1.042–42.205).

Discussion

The present study provided valuable insights into the clinical characteristics and prognostic risk factors of IE patients in recent years on the basis of data collected from a tertiary hospital in China.

This study identified fever and heart murmur as the most common manifestations in IE patients, followed by chest tightness/asthma. Although these findings could occur in various diseases and were nonspecific, IE should be highly suspected when they crossed or coexisted. Consistent with other reports, CHD replaced RHD as the most common

underlying heart disease in IE patients, comprising 20.1%–36.7%^{15–18} of the heart diseases. This percentage might be attributed to the increasing trend of CHD patients in recent years; the late diagnosis for CHD contributed to the restrictions of local medical and economic conditions and a greater number of patients with CHD surviving to adulthood.^{15,19} The main types of IE in patients with CHD were bicuspid aortic valve and ventricular septal defect. Studies further have suggested that the proportion of IE in patients without underlying heart disease is rising, which may be related to the increase of invasive medical measures, hemodialysis, intravenous drug users, and the wide application of antibacterial drugs and immunosuppressants.²⁰ IE has occurred predominantly in males, with a male-to-female ratio of 1.2–2.7:1,²¹ and has been associated with an increased proportion of valvular disease (such as CHD, particularly the bicuspid aortic valve).^{22,23} In the present study, the most frequent complications observed were cerebrovascular accident, splenomegaly, and decreased cardiac function. In the ESC-EORP EURO-ENDO (European infective endocarditis) registry, the most common complications are embolic events (particularly in the brain) in up to 40% of IE patients.²⁴

Therapeutic schedules mainly rely on blood culture, the major criterion for IE, followed by identification and susceptibility testing of the isolate.²⁵ Consistent with previous reports in China,^{26,27} *Streptococcus* was the primary causative organism in IE, followed by *S. aureus*, CoNS, and *Enterococcus*. Owing to population aging, a decrease in RHD burden, and advanced device management, the prevalence of *S. aureus* has increased, eventually becoming the dominant pathogen in IE in developed countries.^{21,28} In the current study, *S. aureus* had a detection rate of only 7.5% but nonetheless was the main cause of septic shock and intracranial infection related to the prognosis of IE patients. *Enterococcus* IE is the third leading cause of IE, ranging in frequency from 7% to 18% in developed countries.^{29–31} However, *Enterococcus* was identified in only 4 patients in this study, and the proportion was similar in another report from East China.²⁰

In the present study, blood cultures were negative in 56.7% of cases, similar to the data in some Asiatic populations (30–61%)^{32–34} but surpassing the number in other developed countries (7–20%).^{33,35,36} The high prevalence of negative blood cultures was usually associated with the antibiotic treatment given before the blood culture, the insufficient number of blood cultures submitted, highly fastidious bacterial or nonbacterial infections, and inadequate microbiological techniques.³⁷ In the present study, 75.0% (102/136) of the patients with negative blood cultures had previous antibiotic therapy. Multiple studies have indicated that previous administration of antibiotics can decrease the recovery rate of bacteria by 35% to 40%,³⁸ particularly against the common bacteria causing IE, such as *Streptococcus*, and less commonly *Staphylococcus* or *Enterococcus*.³⁹ Further, 24 other patients were not tested for blood cultures in our hospital because other medical centers reported negative results, or fewer than two sets of blood cultures were submitted. In addition, serological assessment for special pathogens (eg, *Bartonella*, *C. burnetii*, or *Mycoplasma*) and molecular biological methods (eg, PCR) that had been directly used for clinical microbiology and detection of samples (blood or resected cardiac valves) could be helpful for the diagnosis of IE.²⁵ However, these tests were not conducted in the current study, which was the limitation of this study.

Echocardiography is vital in the diagnosis and evaluation of IE. It detects vegetations in 88.3% of IE patients, with the left heart valves predominantly involved. In this study, the mitral and aortic valves are almost equally affected, with 51.7% and 48.3%, respectively. Multiple valves are involved in 20.4% of cases. These proportions are higher in another report.⁴⁰ In addition, this study found that mitral valve (61.9%) was most commonly involved in RHD patients, while aortic valve (68.6%) was significantly more affected in patients with CHD. In our cohort, the incidence of prosthetic valve endocarditis was only 8.8% (21/240), which is lower than the 26–30% of the cases reported in other studies.^{24,40,41} However, further data indicated that 23 patients had previously undergone cardiac valve replacement or plasty, of which 21 cases developed prosthetic valve infection. Therefore, the prevention of IE in patients undergoing heart valve surgery is the most important.

In the present study, echocardiography failed to detect vegetations in 28 IE patients, but valve vegetations or lesions were found in 20 of them during operation. Transthoracic echocardiography has been shown to exhibit 70% and 50% sensitivity in detecting native valve vegetation and prosthetic valve vegetation, respectively.¹¹ Transoesophageal echocardiography has demonstrated sensitivity and specificity exceeding 90% for vegetations and thus can be performed to confirm the diagnosis of IE in cases of high clinical suspicion, particularly in prosthetic or device-related IE. Additional imaging techniques such as ¹⁸F-FDG PET/CT or radiolabeled leucocyte single-photon emission computed tomography-computed tomography (SPECT-CT) can determine the presence of prosthetic valve infection or perivalvular lesions

(abscess and aneurysm or pseudoaneurysm formation).⁴² In the present study, 2 patients with prosthetic valve-related IE were diagnosed by ¹⁸F-FDG PET/CT.

In our cohort, the mean age of IE patients was 51 y—that is, older than the mean age reported in a study conducted in China from 2013 to 2018.²⁶ Meanwhile, research from developed countries has reported an increasing proportion of elderly patients with IE, which increase stems from multiple factors: more extensive investigations in elderly cases, increased survival in patients with multiple comorbidities, widespread use of invasive therapeutic interventions (such as pacemakers and defibrillators), and hemodialysis.¹⁹ The overall in-hospital mortality rate in our study was 6.3%, but a significantly high mortality rate (18.2%) was observed in the elderly (over 65 y old).

The clinical characteristics of IE patients in different age groups were compared. We found that 30% of IE patients aged less than 50 y had a history of CHD, mainly characterized by splenomegaly, multivalve infection, and paravalvular abscess. By contrast, elderly cases with IE showed lower frequencies of embolic events (particularly splenomegaly) and valvular lesions, as observed in another study.⁷ These patients showed higher occurrences of comorbidities and atrial fibrillation and had poorer prognosis than those of younger patients. Nonspecific features impeded diagnosis in elderly patients. In addition to the common *Streptococcus*, gram-negative bacteria and *Enterococcus* had higher detection rates in elderly patients. Therefore, clinicians should pay attention to the coverage of these pathogens during empiric anti-infective therapy. Early surgery is an effective treatment for patients with IE. However, surgical therapy in elderly patients is less frequently performed because of severe complications and the fear of surgery by patients and their families. Recent studies have demonstrated that many frailty scores can assess the physical condition of elderly patients and the mortality independently of age before cardiac surgery.^{43,44} Treatment success in elderly IE may be improved by comprehensive assessment of patients and cooperation between multiple specialists.

In the present study, the factors associated with increased risk of in-hospital mortality were CHD, previous heart valve surgery, septic shock, atrial fibrillation, infection with gram-negative bacilli, and nonsurgical treatment. Meanwhile, we identified the following as independent risk factors for in-hospital mortality: age over 65 y, intracranial infection, splenic embolization, cerebral hemorrhage, NYHA class III–IV, and prosthetic valve infection. Early identification of patients with high-risk features may contribute to improved outcome through early anti-infective and surgical treatment.⁴⁵ A meta-analysis found that early surgery was associated with reduced in-hospital and long-term mortality, compared with non-early surgery.⁴⁶

This study presents several limitations. First, our study was a retrospective single-center design. The information was limited to medical records and inevitably biased. Second, most patients were transferred to our hospital from other medical centers at the middle or late stage of the disease, resulting in atypical clinical features and negative blood culture results. Moreover, geographic and economic differences existed. With these limitations considered, the subsequent step was to conduct a multicenter prospective cohort study in the region.

Conclusion

This study demonstrates that patients without previous cardiac disease have an increased risk of IE. Attention should be paid to the early diagnosis and treatment of CHD, and the prevention of IE after cardiac valve surgery. *Streptococcus* remains as the primary causative pathogen of IE in developing countries. However, the presence of *S. aureus*, gram-negative bacteria as well as *Enterococci* with a higher prevalence in elderly patients, requires additional consideration by clinicians. Previous antibiotic therapy may be the main cause of a negative blood culture, which is not conducive to the clinical criteria for the diagnosis of IE. Compared with younger patients, elderly patients have more comorbidities and complications but lower rates of surgery, leading to higher in-hospital mortality. On the basis of this finding, the benefits and risks of surgery for elderly patients need to be evaluated via multidisciplinary cooperation. Intracranial infection, splenic embolization, cerebral hemorrhage, NYHA class III–IV, and prosthetic valve infection were identified as independent risk factors for in-hospital mortality in IE patients.

Ethical Statement

Study participants had provided informed consent prior to the start of the study. Written informed consent was provided by the patients' relatives to allow the case details to be published. This study was designed following the Declaration of Helsinki and approved by the ethics committee of Jiangsu Province Hospital.

Disclosure

The authors report no conflicts of interest in this work.

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