A changing profile of infective endocarditis at a tertiary hospital in China: A retrospective study from 2001 to 2018

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Abstract

Background: Infective endocarditis (IE) is a lethal disease which has been changing significantly over the past decades; however, information about IE in China remains scarce. This study surveyed the changes in clinical characteristics of IE at a tertiary hospital in southern China over a period of nearly eighteen years. Methods: Medical records with IE patients consecutively hospitalized between June 2001 and June 2018 were selected from the electronic medical records system in Nanfang Hospital of Southern Medical University. Data were divided by admission time into two groups: early-period group, June 2001 to December 2009 and later-period group, January 2010 to July 2018. Results: A Total of 313 IE patients were included in our study. Compared with the early-period group, patients in the later-period group included fewer intravenous drug users (IVDU), older age at onset, reduced development of pulmonary embolism, less renal dysfunction, decreased proportion of Staphylococcus aureus infection and fewer vegetations observed in the right heart by echocardiography. The later-period group also showed a higher proportion of ischemic strokes and higher rate of whole-blood culture positive compared with the early-period group. The in-hospital mortality rate remained about the same between the two periods. Conclusions: Our study demonstrated a dramatic change in the profile and characteristics of IE over a period of eighteen years at a tertiary hospital in southern China, especially the decrease in intravenous drug users (IVDU), which might be responsible for many other changes.

Background

Infective endocarditis is a lethal disease caused by various pathogens such as bacteria, fungi, and rickettsia that directly invade the cardiac valves or mural endocardium[1]. The profile of IE has been changing significantly over the past decades[2]. Overall, IE related to rheumatic diseases has dramatically decreased in developed countries, being gradually replaced by IE associated with congenital heart disease, degenerative heart valve disease, prosthetic valves and cardiac implantable electronic devices [3]. Staphylococci, which are most often related to healthcare and invasive procedures, have overtaken streptococci as the most common pathogen of IE[4]. The average age of patients has also been increasing[5]. In contrast, rheumatic disease remains a key predisposing factor in developing countries, and streptococci are still the most common cause of IE. In countries with reduced IVDU, right heart IE has also decreased; but in some regions such as eastern Europe, IVDU remains a problem and right-sided IE continues to occur[6]. Many developed countries have a wealth of prospective or retrospective studies for IE [7, 8]. However, there have been few studies of IE in China compared to other countries[9]. To better understand the features of IE and the changes in clinical characteristics at Nanfang Hospital, a tertiary hospital in southern China, we collected and analyzed the data from consecutive cases of IE over a period of 18 year.

Methods

Diagnostic criteria

The definition of cases was based on the European Society of Cardiology (ESC) algorithm for diagnosis of infective endocarditis (2015 edition)[10], which mainly includes the pathological diagnostic criteria and the modified Duke criteria.

Pathological examination served as the gold standard for diagnosing IE, which must meet at least one of the following criteria: microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen or the presence of pathological lesions, vegetation or intracardiac abscesses by histological examination showing active endocarditis.

The modified Duke criteria (adapted from Li et al.[11]) were used for clinical diagnosis with cases classified as either definite or suspected. For a diagnosis of definite IE, the patient must meet two major criteria, or one major criterion and three minor criteria, or five minor criteria. For a diagnosis of suspected IE, the patient must meet one major criterion and one minor criterion or three minor criteria. Major criteria include: (1) blood cultures positive for typical microorganisms consistent with

IE from two separate blood cultures, microorganisms consistent with IE from persistently positive blood cultures or a single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titers >1:800 (2) imaging positive for IE by transthoracic echocardiogram; and (3) definite paravalvular lesions by cardiac CT. Minor criteria include: (1) predisposing heart condition or injection drug use; (2) fever of >38°C; (3) vascular phenomena including those detected by imaging only, major arterial emboli, septic pulmonary infarcts, infectious mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions; (4) immunological phenomena, glomerulonephritis, Osler's nodes, Roth's spots, or rheumatoid factor; (5) microbiological evidence, positive blood culture, but does not meet a major criterion as noted above or serological evidence of active infection with organisms consistent with IE. To exclude misdiagnosed cases as sepsis, non-infective endocarditis and rheumatic myocarditis, suspected patients should either show intracardiac vegetations by echocardiography with an evidence of bacterial infection, or meet the pathological diagnostic criteria.

Health care-associated IE was considered likely if any of the following had occurred: the patient had received intravenous therapy at home, received wound care or specialized nursing care through a health care agency, family, or friends, self-administered intravenous medical therapy in the past thirty days, was examined at a hospital or hemodialysis clinic or received intravenous chemotherapy in the past thirty days, was hospitalized in an acute care hospital for two or more days in the previous ninety days before the infection, or resided in a nursing home or long-term care facility.

Study sample

Nanfang Hospital of Southern Medical University is a large tertiary teaching comprehensive hospital at Guangdong province in southern China with in-patient quantity up to 119,000 statistically in 2018, where surgery quantity in cardiothoracic surgery surpasses 1000 per year. We consecutively collected 313 inpatients diagnosed with IE through the electronic medical records system of Nanfang Hospital between June 2001 and June 2018. The great majority (98.1%) of the patients originated from cities in southern China, such as Guangdong province (79.2%), Hunan province (6.7%), Jiangxi province (4.2%) and Guangxi province (3.5%). They were divided into two groups according to their time of admission: early-period group, from June 2001 to December 2009, and later-period group, from January 2010 to July 2018.

This clinical study was a retrospective and descriptive study consistent with the principles of the Helsinki declaration.

Data included demographic information, predisposing factors, clinical manifestations, laboratory tests including blood work and biochemical measurements, echocardiography results, causative microorganisms, pathologic findings and therapeutic outcomes. The outcomes included improvement at discharge of clinical symptoms, normal laboratory indicators, negative blood cultures and echocardiograms and worsening at discharge with abandonment of treatment because of poor efficacy or death.

Statistical method

All analyses were performed using SPSS version 25.0.0. Continuous variables fitting a normal distribution were expressed as mean ± standard deviation. Categorical variables were expressed as frequency and percentage. Univariate comparisons were evaluated with the use of the independent sample *t* test for continuous variables, and Chi-squared tests or Fisher's exact test for categorical variables, if appropriate. Univariate predictors of in-hospital mortality (P<0.10) were included in the binary logistic regression. The variables included in the final regression models were selected based on a combination of statistical significance (P<0.05) and clinical judgment. The odds ratio (OR) and its 95% confidence interval (CI) were also calculated for each variable in relation to in-hospital mortality. Statistical significance was determined at the 0.05 level.

Results

Basic information

A total of 313 IE patients were consecutively collected in this study, with 97 patients enrolled in the early-period group and 216 patients in the later-period group. Table 1 shows the basic information of the 313 patients (**Table 1**). The later-period group was on average older (44.9 ± 15.4 yrs vs 36.5 ± 15.2 yrs, $P < 0.001$), mainly due to more patients aged 41-60 years old (43.1% vs. 23.7%, OR = 2.433, CI: 1.418-4.174), and fewer patients aged 21-40 (35.2% vs. 56.7%, OR = 0.415, CI: 0.254-0.676). Each group had a similar male-female ratio, approximately 2.6:1. The top five departments that IE patients were admitted to initially were cardiology (28.4%), cardiothoracic surgery (25.6%), infectious disease (15.0%), respiratory (7.7%), and nephrology (5.1%). Our results revealed that the proportion of patients in the respiratory department declined in the later-period group (4.6% vs 14.4%, OR = 0.288, CI: 0.123-0.674). Regarding the factors predisposing to IE, 21 cases (6.7%) were considered as healthcare-associated IE, including three cases in the early-period group and eighteen cases in the later-period group. Heart-based diseases were the dominant predisposing factors (45.4%), including rheumatic heart disease (19.2%), congenital heart disease (16.6%) and degenerative heart valve disease (7.7%). Six (1.9%) cases had more than two kinds of heart disease. The later-period group had fewer intravenous drug users than the early-period group (12.0% vs 25.8%, OR = 0.394, CI: 0.214-0.727). The proportion of diabetic patients was higher in the later-period group, but without statistical significance (10.6% vs. 5.2%).

Manifestations and complications

Table 2 details the manifestations and complications of the 313 IE patients in this study. Our results showed that the two groups had similar clinical features, including fever, heart murmurs, hypoproteinemia, anemia, chest pain, heart insufficiency, embolism and hemorrhagic stroke despite radiographically visible splenomegaly (26.4% vs 15.5%, OR = 1.960, CI: 1.046-3.673) and ischemic (27.3% vs 10.3%, OR = 3.269, CI: 1.592-6.714) stroke, which was more frequently found in later-period group, while pulmonary embolism (1.9% vs 7.2%, OR = 0.243, CI: 0.069-0.849) and renal failure (6.0% vs 15.5 %, OR = 0.350, CI: 0.160-0.768) seemed to appear less often in later-period group. Although the percentage of patients developing emboli increased somewhat, there was no significant difference between the two groups (29.2% vs 19.2%).

Blood culture

All 311 IE patients in our study were subjected to blood culture (BC), while blood culture-negative IE (BCNE) patients accounted for 41.8%. The BCNE rate of the later-period group was lower than that of the earlier group (37.0% vs 52.6%, OR = 1.890, CI: 1.159-3.077). The types of microorganism found in the 181 patients with positive BC results are summarized in **Table 3**. Gram-positive cocci (89.0%) dominated the list, followed by Gram-negative bacilli (6.1%), other bacterial (3.9%) and fungi (3.3%). *Staphylococcus aureus* and Streptococcus were separately the most frequent microorganism in earlier-period group and later-period group. The presence of *Staphylococcus aureus* in the later-period group was less common than in the early-period group (20.0% vs 41.3%, OR = 0.355, CI: 0.172-0.732). Instead, with the exception of *Staphylococcus aureus* and streptococcus, other gram-positive cocci, such as Enterococcus (9.6% vs 2.2%) and *Globicatella Sanguis* (6.7% vs 4.3%), got a notably increase (27.4% vs 13.0%, OR=2.517, CI: 0.985-6.429) in later-period group.

Echocardiography

All patients underwent a transthoracic echocardiography (TTE) examination and 274 (87.5%) showed positive results (**Table 4**). There were significantly more negative results in the later-period group than in the early-period group (15.3% vs 6.2%, OR = 2.735, CI: 1.106-6.764). Among the positive cases, 199 (63.6%) showed vegetations on the left heart valves, 60 (19.2%) cases were right-sided, 9 (2.9%) cases were on both sides, and 6 cases developed vegetations on non-valvular endocardium. A lower percentage of patients in the later-period group showed right-heart vegetations (16.2% vs 25.8%, OR = 0.557, CI: 0.311-0.996), especially on the tricuspid valve (14.8% vs 24.7%, OR = 0.529, CI: 0.292-0.959).

Outcomes and predictors of in-hospital mortality

All patients received antibiotic therapy, with 187(59.7%) submitted to surgery treatment. The surgery rate between two groups appeared to be similar **(Table 5)**.

A total of 35 patients (11.2%) died in hospital, 11 in the early-period group and 24 in the later-period group. Of these, 14 died from acute heart failure, 10 from cerebrovascular events, 9 from septic shock and multiple organ failure, and 1 each from severe arrhythmia and acute myelitis. There was no significant difference in in-hospital mortality between two groups.

Multivariate analysis of the clinical variables found to have statistical significance in the univariate analysis（**Table 6**） identified the following as independent predictors of in-hospital mortality: prosthetic valve endocarditis (OR=11.464, CI: 1.759-74.719), intravenous drug addicted (OR=6.047, CI: 1.451-25.197), hemorrhagic stroke (OR=7.234, CI: 2.129-24.581), congestive heart failure (OR=8.233, CI: 2.935-23.098), renal insufficiency (OR=7.926 CI: 2.481-25.319), left-sided endocarditis (OR=5.532, CI:1.319-23.193), fungal endocarditis (OR=13.343, CI: 1.424-125.305) and surgical treatment (OR=0.155, CI: 0.054-0.450) （**Table 7**）. Age>40 years, sex, health care-related endocarditis, embolism, ischemic stroke, hypoproteinemia and *Staphylococcus aureus* endocarditis are not independent determinants of in-hospital mortality. The goodness-of-fit of the multivariable model was determined by Hosmer–Lemeshow test (Chi-square = 6.542, P = 0.478).

Discussion

IE is a fatal disease with diversity of clinical manifestations and risk factors, continuing to be associated with high mortality despite of novel diagnostic and therapeutic strategies[1]. The demographics, predisposing factors, clinical features, and microbiological spectrum of IE have evolved in recent decades. Relative studies remain scarce in China, and are usually of small sample. Our study was aimed to better understand the regional characteristics and the changing profile of IE over 18 years in our hospital, and to evaluate independent factors that influence the outcome of IE. To our knowledge, this is the largest study on IE performed in our region over 18 years.

Clinical features

The proportion of IVDUs declined by half in later-period group(12.0% vs 25.8%, OR = 0.394, CI: 0.214-0.727) as the Chinese government had been stepping up efforts to crack down drug cartels[12], which might serve as the most important reason for changes of profile of IE for 18 years.

Firstly, patients with IE in the later-period group became older than those from the early-period group (44.9 ± 15.4 vs 36.5 ± 15.2, P<0.001), which was roughly similar to that reported in neighboring regions [9, 13, 14], but far younger than those in developed countries [15-17]. The upward tendency of onset age was probably related to the downward trend of intravenous drugs abusing. Compared with middle-aged and elderly people, young adults are more likely to be exposed to drugs[18, 19]. In addition, the decrease of patients with rheumatic heart disease (from 22.7% to 17.6%) and the increase with degenerative heart disease (from 4.1% to 9.3%), may lead to an increase in patients' age.

Secondly, the positive rate of *Staphylococcus aureus* decreased strikingly in the later-period group (20.0% vs 41.3%, OR = 0.355, CI: 0.172-0.732), while the echocardiography results showed a lower proportion of tricuspid valve vegetations in the later-period group, which is linked to the significantly lower proportion of IVDU since it is generally known that IVDU-related IE is more likely to involve *Staphylococcus aureus* and infection of the tricuspid valve[18, 20]. By comparison, the increase of other gram-positive cocci might be attributed to the relatively uprising of other predisposing factors besides IVDU.

Thirdly, IE patients of the later-period group developed less ischemic stroke (27.3% vs 10.3%, OR = 3.269, CI: 1.592-6.714). Previous studies reported that *Staphylococcus aureus* infection and vegetations on the mitral valve were risk factors for ischemic stroke[21, 22], but among the patients in this study, the later-period group showed a lower percentage of *Staphylococcus aureus* infection and a nonsignificant rise in patients with mitral vegetations (34.7% vs 30.9%). We speculate that an older age at onset and a higher proportion of diabetics (10.6% vs 5.2%) may play a more important role in triggering ischemic stroke.

Besides, the decrease of patients with pulmonary embolism (1.9% vs 7.2%, OR = 0.243, CI: 0.069-0.849) in the later-period group could be explained by less numerous right-sided IE. Also, the lower occurrence of renal insufficiency (6.0% vs 15.5 %, OR = 0.350, CI: 0.160-0.768) might be benefitting from the reduction in *Staphylococcus aureus* infection and the downward trend in cardiac insufficiency (56.5% vs 61.9%) in recent years[23].

Above all, the IVDU played an important role in the changing profile of IE. Beyond the IVDU-related IE, there were still some other points below worth mentioning.

The negative echocardiography results (absence of vegetations) were seen to increase significantly in the later-period group (15.3% vs 6.2%, OR = 2.735, CI: 1.106-6.764). The most frequent explanations for a negative echocardiogram are very small vegetations, non-oscillating and/or atypically located vegetations, or severe, pre-existing lesions from rheumatic heart disease or degenerative heart disease in heart valves[24]. IE Patients in the later-period group had a higher proportion of degenerative valvular heart disease (9.3% vs 4.1%), which manifested as high-density calcification on echocardiograms and was hard to distinguish from vegetations. Also, the overuse of antibiotics may shrink the vegetations, making them difficult to identify by echocardiography.

Splenomegaly was more frequently found in the later-period group (26.4% vs 15.5%, OR = 1.960, CI: 1.046-3.673). This phenomenon had not previously been seen in previous reports, perhaps owing to the development of improvements in imaging technology.

Up to 41.8% of patients were blood-culture negative in our study, which was similar to other region of China(from 31.4% to 51%)[9, 14, 25], far higher than that reported in western countries [5, 15]. Blood culture-negative infective endocarditis is associated with inappropriate antibiotic treatment, faulty culture techniques, atypical pathogens that are difficult to culture or identify[26]. Among these factors, the misuse and overuse of antibiotics remained a problem, especially for patients with long-term fever. The majority (93.1%) of the BCNE patients in our study received empiric antibiotic treatment prior to etiological examination. Atypical pathogens can be identified by serological analysis and polymerase chain reaction (PCR) assays of blood and pathological specimens[27], which is difficult to realize in clinical practice due to economic and subjective factors. With the development of improved microbial culture techniques, increased medical expertise, and more accurate specifications for the diagnostic and treatment processes, the negative blood-culture rate achieved a remarkable decline in the later-period group (37.0% vs 52.6%, OR = 1.890, CI: 1.159-3.077); still, there is room for improvement and research efforts need to be continued.

A systematic review of 21 regional literatures in the world revealed that the average fatality rate of IE is 21.1% ± 10.4%[2]. The in-hospital mortality of our study was 11.2%, nearly approaching to the lower limit and quite similar to another research conducted in East China (10.9%). Moreover, it is noteworthy that even with the novel diagnostic and therapeutic strategies available now, the in-hospital mortality did not strikingly differ between the two groups, which means minimizing the in-hospital mortality of IE is still a long-term undertaking.

Risk factors for in-hospital mortality

To explore the independent risk factors for in-hospital mortality, we performed a backward stepwise logistic regression analysis model. The results indicated that health care-related endocarditis[6, 28], prosthetic valve endocarditis[6, 29], intravenous drug users, hemorrhagic stroke, congestive heart failure[14, 30-32], renal insufficiency[30], left cardiac valve vegetations, fungal endocarditis, surgical treatment[6, 32-34] were the independent determinants of in-hospital mortality. Many of them are consistent with conclusions of previous research. But some factors such as age, sex, embolism, although it showed a high influence on in-hospital mortality in univariate analysis, was finally ruled out from multivariate analysis model. It was clearly different from results of previous studies[14, 28, 35]. Perhaps multifarious confounding factors contributed to their analysis results.

Early surgery during antibiotic therapy is a protective factor for prognosis of IE in our study. Mortality of patients who underwent surgery was one sixth of that of patients who did not have the surgery(OR=0.155, CI: 0.054-0.450). In our study, up to 59.7% of our patients underwent valve surgery during the initial hospitalization, which is relative high compared to results observed in other countries[6, 31]. We believe that good standard of care in our hospital, and relatively younger age were a major reason for patients to make aggressive decision of surgical treatment. And we speculated that the relatively lower in-hospital mortality compared to foreign countries, may be mainly contributed by higher rate of surgical treatment and younger age of onset.

It seems that the independent link of intravenous drug users, hemorrhagic stroke, left-sided endocarditis and fungal endocarditis to in-hospital mortality has not yet been pointed out before. The mortality of IVDU-related IE had been reported to be lower than that in none-IVDU-related IE in some studies[36], which was poles apart from our conclusion. Hemorrhagic stroke itself is exactly a highly lethal disease. Left-sided endocarditis was described as independent risk factor for mortality of IVDU-related IE, but not of IE[37]. The fungal endocarditis in our study was of extremely small sample (only 6 of 313) so its veracity of statistical significance deserve suspicion. Consequently, further studies are essential for validation of our conclusions.

limitation

This study focused on a single-center in a general teaching hospital without long-term follow-up. Most patients came from south China, thus findings in this study may not be applicable to all populations. Besides, referral bias should be taken into consideration when describing the clinical spectrum and outcome of IE, as patients with more complications such as stroke, heart failure and new valvular regurgitation and surgery indications, who are more likely to be gravely ill patients, are more likely to choose a tertiary hospital[38]. So our conclusions may not apply to small hospital. However, our observations reflected a dynamic change of IE in our center over a period of eighteen consecutive years with a relatively large sample size, while relative study remains scarce in China. The geographic variations observed in our study will be of important value to profile the clinical feature of China and offer the reference for clinical decisions in our region.

Conclusion

In conclusion, intravenous drug abuse was less common in later-period group, which might result in a series of changes like older age of onset, fewer pulmonary embolism, renal failure, *Staphylococcus aureus* endocarditis and right-sided IE. More ischemic stroke was observed possibly due to older age. Also, patience in later-period showed more splenomegaly, lower BCNE rate and negative echocardiography results. The in-hospital mortality stayed still despite of the changing profile of IE. The multivariate analysis underlined the significance of prosthetic valve endocarditis, intravenous drug addicted, hemorrhagic stroke, congestive heart failure, renal insufficiency, left-sided endocarditis, fungal endocarditis and surgical treatment to in-hospital mortality.

Abbreviations

IE: Infective endocarditis; IVDU: Intravenous drug users; ESC: European Society of Cardiology; OR: Odds ratio; CI: Confidence interval; PCR: Polymerase chain reaction; FDG: Fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed Tomography; SPECT: Single-photon emission computed tomography; BC: Blood culture; NCBC: Blood culture-negative infective endocarditis; TTE: Transthoracic echocardiography.

Declarations

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Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Study conception and design: JP and ZNR. Acquisition, analysis and/or interpretation of data: ZNR. Drafting/revision of the work for intellectual content and context: JP, ZNR, XCM and HJC. Final approval and overall responsibility for the published work: JP. All of the authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the clinical research ethics committee of Nanfang Hospital of Southern Medical University. This was a retrospective study that did not need informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Tables

Table 1 Patient characteristics.

Variable	Total	Early-period group	Later-period group	*P*	OR	95%CI	
	N=313	N=97	N=216			Lower	Upper
Age(year)	42.3 ± 15.8	36.5 ± 15.2	44.9 ± 15.4	< 0.001*		4.692	12.064
≤20	18 (5.8)	9 (9.3)	9 (4.2)	0.072			
21-40	131 (41.9)	55 (56.7)	76 (35.2)	< 0.001	0.415	0.254	0.676
41-60	116 (37.1)	23 (23.7)	93 (43.1)	0.001	2.433	1.418	4.174
≥61	48 (15.3)	10 (10.3)	38 (17.6)	0.098			
Male	226 (72.2)	70 (72.2)	156 (72.2)	0.992			
Admission departments							
Department of Cardiology	89 (28.4)	26 (26.8)	63 (29.2)	0.668			
Department of Cardiothoracic Surgery	80 (25.6)	19 (19.6)	61 (28.2)	0.105			
Department of Infectious Disease	47 (15.0)	10 (10.3)	37 (17.1)	0.118			
Department of Respiratory	24 (7.7)	14 (14.4)	10 (4.6)	0.003	0.288	0.123	0.674
Department of Nephrology	16 (5.1)	8 (8.2)	8 (3.7)	0.158			
Predisposing factors							
Health care-related	21 (6.7)	3 (3.1)	18 (8.3)	0.087			
Basic heart disease	142 (45.4)	47 (48.5)	95 (44.0)	0.462			
Congenital heart disease	52 (16.6)	20 (20.6)	32 (14.8)	0.202			
Rheumatic heart disease	60 (19.2)	22 (22.7)	38 (17.6)	0.290			
Degenerative heart valve disease	24 (7.7)	4 (4.1)	20 (9.3)	0.114			
Multiple heart disease	6 (1.9)	1 (1.0)	5 (2.3)	0.749			
Intravenous drug users	51 (16.3)	25 (25.8)	26 (12.0)	0.002	0.394	0.214	0.727
Prosthetic valve replacement	11 (3.5)	3 (3.1)	8 (3.7)	0.952			
Previous IE history	8 (2.6)	2 (2.1)	6 (2.8)	0.987			
Recent skin infection	10 (3.2)	3 (3.1)	7 (3.2)	0.781			
Diabetes	28 (8.9)	5 (5.2)	23 (10.6)	0.115			

Age is presented as mean ± standard deviation. Other variables are presented as count (%). *P* value were estimated by *independent sample *t* test or Chi-squared tests . One patient could have two or more underlying predisposing factors.

Table 2 Manifestations and complications of 313 patients

Variable	Total	Early-period group	Later-period group	*P*	OR	95%CI	
	N=313	N=97	N=216			Lower	Upper
Manifestations							
Fever	262 (83.7)	81 (83.5)	181 (83.8)	0.949			
Cardiac murmurs	262 (83.7)	87 (89.7)	175 (81.0)	0.055			
Splenomegaly	72 (23.0)	15 (15.5)	57 (26.4)	0.034	1.960	1.046	3.673
Chest pain	38 (12.1)	14 (14.4)	24 (11.1)	0.405			
Janeway lesion	11 (3.5)	6 (6.2)	5 (2.3)	0.165			
Osler nodes	5 (1.6)	3 (3.1)	2 (0.9)	0.354			
Laboratory tests							
Leukocytosis or neutrophilia	199 (63.6)	64 (66.0)	135 (62.5)	0.554			
Anemia	243 (77.6)	76 (78.4)	168 (77.8)	0.910			
Hypoproteinemia	291 (93.0)	87 (89.7)	203 (94.0)	0.178			
Complications							
Heart insufficiency	182 (58.1)	60 (61.9)	122 (56.5)	0.373			
Embolism	82 (26.2)	19 (19.6)	63 (29.2)	0.075			
Ischemic stroke	69 (22.0)	10 (10.3)	59 (27.3)	<0.001	3.269	1.592	6.714
Pulmonary embolism	11 (3.5)	7 (7.2)	4 (1.9)	0.040	0.243	0.069	0.849
Splenic infarction	7 (2.2)	3 (3.1)	4 (1.9)	0.785			
Renal infarction	20 (6.4)	4 (4.1)	16 (7.4)	0.272			
Hemorrhagic stroke	27 (8.6)	7 (7.2)	20 (9.3)	0.552			
Metastatic abscess	19 (6.1)	6 (6.2)	13 (6.0)	0.954			
Pulmonary abscess	14 (4.5)	4 (4.1)	10 (4.6)	0.924			
Cerebral abscess	7 (2.2)	3 (3.1)	4 (1.9)	0.785			
Renal insufficiency	28 (8.9)	15 (15.5)	13 (6.0)	0.007	0.350	0.160	0.768
No complications	27 (8.6)	9 (9.3)	18 (8.3)	0.783			

Variables are presented as count (%). *P* value were estimated by Chi-squared tests. One patient could have two or more manifestations and complications.

Table 3 Microorganism found in the 181 patients with positive blood culture results

Variable	Total	Early-period group	Later-peirod group	*P*	OR	95%CI	
	N=181	N=46	N=135			Lower	Upper
Gram-positive cocci	161 (89.0)	40 (87.0)	121 (89.6)	0.618			
Staphylococcus aureus	46 (25.4)	19 (41.3)	27 (20.0)	0.004	0.355	0.172	0.732
Streptococcus	76 (42.0)	17 (37.0)	59 (43.7)	0.423			
Other	43 (23.8)	6 (13.0)	37 (27.4)	0.048	2.517	0.985	6.429
Enterococcus	14 (7.7)	1 (2.2)	13 (9.6)	0.188			
Globicatella Sanguis	11 (6.1)	2 (4.3)	9 (6.7)	0.833			
Gram-negative bacilli	11 (6.1)	1 (2.2)	10 (7.4)	0.355			
Other bacterial	7 (3.9)	2 (4.3)	5 (3.7)	0.805			
Fungi	6 (3.3)	3 (6.5)	3 (2.2)	0.352			

Variables are presented as count (%). *P* value were estimated by Chi-squared tests . One patient could be isolated two or more kinds of causative microorganisms from blood culture..

Table 4 Echocardiography results of 313 patients

Variable	Total	Early-period group	Later-period group	*P*	OR	95%CI	
	N=313	N=97	N=216			Lower	Upper
Vegetation							
No vegetation	39 (12.5)	6 (6.2)	33 (15.3)	0.024	2.735	1.106	6.764
Left cardiac valve	199 (63.6)	60 (61.9)	139 (64.4)	0.671			
Mitral valve	105 (33.5)	30 (30.9)	75 (34.7)	0.511			
Aortic valve	72 (23.0)	23 (23.7)	49 (22.7)	0.842			
Mitral and aortic valve	22 (7.0)	7 (7.2)	15 (6.9)	0.931			
Right cardiac valve	60 (19.2)	25 (25.8)	35 (16.2)	0.047	0.557	0.311	0.996
Tricuspid valve	56 (17.9)	24 (24.7)	32 (14.8)	0.034	0.529	0.292	0.959
Pulmonary valve	4 (1.3)	1 (1.0)	3 (1.4)	0.777			
Both left and right cardiac valve	9 (2.9)	2 (2.1)	7 (3.2)	0.833			
Peripheral abscess	14 (4.5)	5 (5.2)	9 (4.2)	0.924			
Severe regurgitation	190 (60.7)	57 (58.8)	133 (61.6)	0.638			

Variables are presented as count (%). *P* value were estimated by Chi-squared tests .

Table 5 Outcomes of 313 IE patients

iable	Total				Early-period group				Later-period group				P
	N=313				N=97				N=216				
atment regimen													
ntibiotic plus jery	187	(	59.7	)	57	(	58.8	)	130	(	60.2	)	0.812
th	35	(	11.2	)	11	(	11.3	)	24	(	11.1	)	0.953
cute heart failure	14	(	4.5	)	4	(	4.1	)	10	(	4.6	)	0.924
erebrovascular its	10	(	3.2	)	3	(	3.1	)	7	(	3.2	)	0.781
eptic shock and tiple organ failure	9	(	2.9	)	5	(	5.2	)	4	(	1.9	)	0.211
thers	2	(	0.6	)	1	(	1.0	)	1	(	0.5	)	0.575†

ables are presented as count (%). *P* value were estimated by Chi-squared tests or †Fisher exact tests.

Table 6 Factors associated with in-hospital mortality: univariate analysis

Factor	Category	Number	Deaths（%）	Odds ratio	95%CI lower	95%CI upper	*P*
Basics							
Age	<40	149	11 (7.38)	0.465	0.219	0.986	0.042
	>=40	164	24 (14.63)				
Sex	male	226	32 (14.16)	4.619	1.376	15.501	0.007
	female	87	3 (3.45)				
Health care-related	yes	21	7 (33.33)	4.714	1.756	12.654	0.003
	no	292	28 (9.59)				
Intravenous drug users	yes	51	10 (19.61)	2.312	1.034	5.171	0.037
	no	262	25 (9.54)				
Clinical findings							
Hemorrhagic stroke	yes	27	10 (37.04)	6.141	2.541	14.840	<0.001
	no	286	25 (8.74)				
Embolism	yes	82	15 (18.29)	2.362	1.145	4.870	0.017
	no	231	20 (8.66)				
Ischemic stroke	yes	69	14 (20.29)	2.703	1.292	5.653	0.007
	no	244	21 (8.61)				
Heart insufficiency	yes	182	27 (14.84)	2.678	1.175	6.103	0.016
	no	131	8 (6.11)				
Acute congestive heart failure	yes	67	21 (31.34)	7.565	3.586	15.961	<0.001
	no	246	14 (5.69)				
Renal insufficiency	yes	28	12 (42.86)	8.543	3.610	20.217	<0.001
	no	285	23 (8.07)				
Albumin	<30g/L	147	24 (16.33)	2.747	1.297	5.848	0.007
	>30g/L	166	11 (6.63)				
Microorganism							
Blood culture	Positive	181	25 (13.81)	1.955	0.905	4.225	0.084
	Negative	132	10 (7.58)				
Staphylococcus aureus	yes	46	9 (19.57)	2.255	0.980	5.188	0.051
	no	267	26 (9.74)				
Fungi	yes	6	3 (50.00)	8.594	1.664	44.375	0.002†
	no	307	32 (10.42)				
Echocardiography							
Vegetation	Negative	39	0 (0.00)	1.146	1.096	1.200	0.036
	Positive	181	35 (19.34)				
Left heart	yes	199	28 (14.07)	2.503	1.056	5.931	0.032
	no	114	7 (6.14)				
Valve type	Prosthetic	11	4 (36.36)	4.995	1.384	18.029	0.027
	Native	302	31 (10.26)				
Surgery treatment	yes	187	9 (4.81)	0.194	0.088	0.431	<0.001
	no	126	26 (20.63)				

P value were estimated by Chi-squared tests or †Fisher exact tests.

Multivariate predictors of in-hospital mortality

	B	Odds ratio	95%CI		*P*
			lower	upper	
40					0.208
					0.177
care-related endocarditis	1.598	4.945	1.191	20.527	0.028
etic valve endocarditis	2.439	11.464	1.759	74.719	0.011
nous drug users	1.800	6.047	1.451	25.197	0.013
ism					0.676
nic stroke					0.282
hagic stroke	1.979	7.234	2.129	24.581	0.002
congestive heart failure	2.108	8.233	2.935	23.098	0.002
nsufficiency	2.070	7.926	2.481	25.319	<0.001
roteinemia					0.109
diac valve vegetations	1.711	5.532	1.319	23.193	0.019
endocarditis	2.591	13.343	1.421	125.305	0.023
lococcus aureus endocarditis					0.145
treatment	-1.862	0.155	0.054	0.450	0.001

factors were excluded from the final multivariate analysis model

Figures

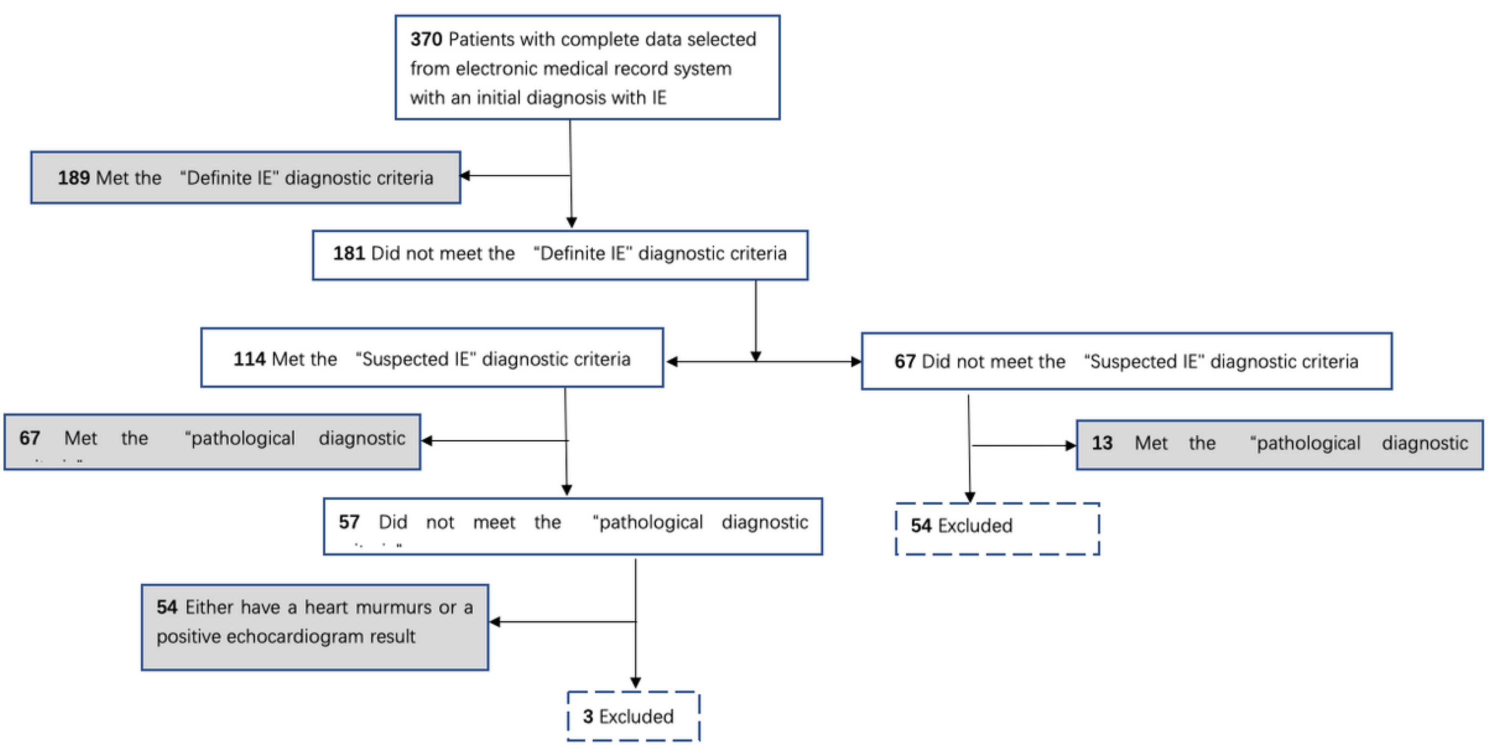

Figure 1

Screening process for IE patients

Supplementary Files

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- Table5.jpg