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 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 at 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 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. The average age of patients has also been increasing[4]. 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[5]. Many developed countries have a wealth of prospective or retrospective studies for IE [6, 7]. However, there have been few studies of IE in China compared to other countries[8]. To better understand the features of IE and the changes in clinical characteristics in southern China, we collected and analyzed the data from consecutive cases of IE over a period of 18 years in Nanfang Hospital.

Methods

Diagnostic criteria

The definition of cases was based on the European Society of Cardiology (ESC) algorithm for diagnosis of infective endocarditis (2015 edition)[9], 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.[10]) 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. To exclude misdiagnosed cases, suspected patients must at least have a heart murmurs or a positive echocardiogram result.

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 >1:80; (2) imaging positive for IE including an echocardiogram, 18F-FDG PET/CT or SPECT/CT, or cardiac CT; 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.

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 population

A total of 370 inpatients diagnosed with IE were selected through the electronic medical records system of Nanfang Hospital of Southern Medical University, a general teaching hospital whose patients mostly came from Guangdong, Guangxi, Hunan and Jiangxi provinces in southern China between June 2001 and June 2018. Sixty-seven patients were excluded, of which 57 did not meet the diagnostic criteria.

The screening process is shown in Figure 1. The remaining 313 IE patients were divided into two groups according to their time of admission: early-period, from June 2001 to December 2009, and later-period, from January 2010 to July 2018.

This clinical study was a retrospective 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 analysis

Continuous variables fitting a normal distribution were expressed as mean ± standard deviation. Categorical variables were expressed as frequency and percentage. When comparing data between two groups, an independent sample *t* test was used for continuous variables, while Chi-squared tests or Fisher exact tests were used for categorical variables, if appropriate. All analyses were performed using SPSS version 25.0.0. The level of significance for all statistical tests was 2-sided, with significance value defined as $P < 0.05$. An odds ratio(OR) and 95% confidence interval (95%CI) were presented when a $P < 0.05$.

Results

Basic information

A total of 313 IE patients were included 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%, $P = 0.001$, OR = 2.433), and fewer patients aged 21-40 (35.2% vs. 56.7%, $P< 0.001$, OR = 0.415). 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%, $P = 0.003$, OR = 0.288). 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%, $P = 0.002$, OR = 0.350).

The proportion of diabetic patients was higher in the later-period group, but without statistical significance (10.6% vs. 5.2%, *P* = 0.115).

Manifestations and complications

Table 3 details the manifestations and complications of the 313 IE patients in this study. Our results showed that the two groups had similar clinical features (**Table 2**), including fever (83.7%), heart murmurs (83.7%), hypoproteinemia (93.0%), anemia (77.6%), chest pain (12.1%), heart insufficiency (58.1%), embolism (26.2%), radiographically visible splenomegaly (23.0%), and hemorrhagic stroke (8.6%). Ischemic (27.3% vs 10.3%, *P* < 0.001, OR = 3.269) stroke and splenomegaly (26.4% vs. 15.5%, *P* = 0.034, OR = 1.960) were more frequently found in the later-period group, while pulmonary embolism (1.9% vs 7.2%, *P* = 0.040, OR = 0.243) and acute renal failure (6.0% vs 15.5 %, *P* = 0.007, OR = 0.350) seemed to appear less often in patients of the later group. Although the percentage of patients developing emboli increased somewhat, there was no significant difference between the two groups (29.2% vs 19.2%, *P* = 0.075).

Blood culture

All 311 IE patients in our study were subjected to blood culture (BC), and 181 (58.2%) showed positive results, 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 (37.5% vs 52.6%, *P* = 0.012, OR = 0.541). 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%). The presence of *Staphylococcus aureus* in the later group was less common than in the later-period group (20.0% vs 41.3%, *P* = 0.004, OR = 0.355). Instead, with the except 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%, *P*=0.048, OR=2.517).

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%, *P* = 0.024, OR = 2.735). 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%, *P* = 0.047, OR = 0.557), especially on the tricuspid valve (14.8% vs 24.7%, *P* = 0.034, OR = 0.529).

Outcomes

All patients received standard therapy, with 187(59.7%) choosing antibiotic treatment plus surgery and 126 (33.9%) preferring antibiotics only. The antibiotic plus surgery regimen resulted in better outcomes than antibiotic treatment alone (94.7% vs 30.2%, *P*<0.001). The effective rate of each treatment regimen between the 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 death rate between two groups.

Discussion

The demographics, predisposing factors, clinical features, and microbiological spectrum of IE have all evolved in recent decades. Our study showed that in contrast with Chinese IE patients from the earlier time period, the clinical features in those from the later-period reflected the effects of older age at onset and less IVDU, and included similar manifestations despite more splenomegaly, fewer pulmonary embolisms and less renal dysfunction, but more complications from ischemic stroke. Also, the incidence of *Staphylococcus aureus* represented in the increased BC-positive rate was significantly decreased in the later-period group. Echocardiography showed that this group had fewer vegetations on the right heart.

IE has a well-recognized and consistent male predominance[11], although some studies[12] did show a gradually increasing rate in females. Among the 313 IE patients in this study, the male-female ratio remained 2.6:1 over the 19-year period. Patients in the later-period group were 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 [8, 13, 14], but far younger than in developed countries [5, 12, 15]. The upward tendency of onset age was mainly reflected in the increase of patients aged 41-60 (43.1% vs 23.7%, $P = 0.001$, 0R = 2.433) and the reduction of patients aged 21-40 (35.2% vs 56.7%, $P<0.001$, OR = 0.415), which was probably related to the proportion of IVDUs. Compared with middle-aged and elderly people, young adults are more likely to be exposed to drugs[16]. The use of intravenous drugs has been declining year by year in our country after the government launched a series of policies against drug use[17]. Our study supported this conclusion because the percentage of IE patients who had been drug users decreased in the later-period group (12.0% vs 25.8%, $P = 0.002$, OR = 0.394), which was possibly responsible for the upward trend of the average onset age. In addition, the decrease in rheumatic heart disease from 22.7% to 17.6% and the increase in degenerative heart disease from 4.1% to 9.3%, although not significant, may lead to an increase in patients' age.

Bacterial infection, cardiac signs and vascular embolism events, usually presenting as fever, heart murmurs and emboli to the brain, lung, spleen or kidney, are the three major clinical features of IE patients[5]. In our study, fever, heart murmurs and embolic complications at the time of diagnosis accounted for 83.7%, 83.7% and 26.2% of patients respectively, which was similar to the data of the ESC guidelines[9].

The occurrence of splenomegaly is mainly due to bacteremia, and long-term stimulation of circulating immune complexes, leading to the proliferation of reticuloendothelial cells. We found that splenomegaly was more frequent in the later-period group (26.4% vs 15.5%, $P = 0.034$, OR = 1.960). This phenomenon had not previously been seen in domestic and foreign reports, owing perhaps to the development of improvements in imaging technology.

Ischemic stroke is one of the most common central nervous events in IE patients, and occurred in 22% of the patients in our study, and was more common in the later-period group (27.3% vs 10.3%, $P = 0.001$, OR = 3.269). It has been reported that *Staphylococcus aureus* infection and vegetations on the mitral valve were risk factors for ischemic stroke [18, 19], but among the patients in this study, the later-period group showed a lower percentage of *Staphylococcus aureus* infection (20.0% vs 41.3%, $P = 0.004$, OR = 0.355) and a nonsignificant rise in patients with mitral vegetations (34.7% vs 30.9%). We speculate that a significantly 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. Pulmonary embolism occurs when blood clots break off from vegetations on right-sided endocardium or valves. The decrease of pulmonary embolism in the later-period group (1.9% vs 7.2%, $P = 0.040$, OR = 0.243) could be explained by less numerous right-sided IE compared to the early-period group (16.2% vs 25.8%, $P = 0.047$, OR = 0.557).

The decrease in pulmonary embolism may be responsible for the lower number of patients admitted to the respiratory department initially in the later-period group (4.6% vs 14.4%, $P = 0.003$, OR = 0.288). Some studies revealed that chronic heart failure, *Staphylococcus aureus* infection, and coagulase-negative staphylococci were associated with a high risk of renal failure[20].

Acute renal insufficiency was lower in the later-period group (6.0% vs 15.5%, $P = 0.007$, OR = 0.350), which may be benefitting from the reduction in *Staphylococcus aureus* infection and the downward trend in cardiac insufficiency (56.5% vs 61.9%) in recent years.

Blood culture-negative infective endocarditis is associated with inappropriate antibiotic treatment, faulty culture techniques, atypical pathogens that are difficult to culture or identify such as *Mycoplasma*, *Legionella*, and *Bartonella*, and fungal endocarditis[21]. In this study, up to 40.5% of patients were blood-culture negative, which was far higher than that reported in western countries [4, 5]. Among these factors, the misuse and overuse of antibiotics remained a problem, especially for patients with long-term fever. Atypical pathogens can be identified by serological analysis and polymerase chain reaction (PCR) assays of blood and pathological

specimens[22], 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 (37.5% vs 52.6%, *P* = 0.012, OR = 0.541); still, there is room for improvement and research efforts need to be continued.

Gram-positive cocci were the predominant species among causative pathogens, accounting for 89.0% of all detected microorganisms, far ahead of the number of cases caused by Gram-negative bacilli (6.1%) and fungi (3.3%). *Streptococcus* (42.0%) and *Staphylococcus aureus* (25.4%) remain the most common pathogens. The incidence of *Staphylococcus aureus* decreased strikingly in the later-period group (20.0% vs 41.3%, *P* = 0.004, OR = 0.355), while the echocardiography results showed a lower proportion of tricuspid valve vegetations in the later-period group. This may be 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[16, 23]. Therefore, as mentioned above, the reduced proportion of IVDU in recent years may indirectly contribute to the downward trend of *Staphylococcus aureus* infection and right-sided IE. By comparison, the increase of other gram-positive cocci (27.2% vs 13.0%, P=0.048, OR=2.517) might be attributed to the relatively uprising of other predisposing factors besides IVDU.

The vegetations visible by echocardiography are the hallmark lesions of IE. However, negative echocardiography results (absence of vegetations) were also seen to increase significantly in the later-period group (15.3%vs 6.2%, *P* = 0.024, OR = 2.735). It is well-known that a negative echocardiographic examination does not rule out IE, and the sensitivity of TTE for the diagnosis of vegetations is about 75%. 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, resulting in false negative results. In addition, the overuse of antibiotics may shrink the vegetations, making them difficult to identify by echocardiography.

A systematic review of twenty-one regional literatures in the world revealed that the average fatality rate of IE is 21.1% ± 10.4%[2], while the mortality rate of our study was 11.2%, approaching the lower limit. The results did not represent a high cure rate of IE because only the in-hospital mortality rate was calculated in our study without follow-up data. Some patients may have died after discharge. As a retrospective study, the time span was too large and the survival data of this part of the population was missing. Even with the novel diagnostic and therapeutic strategies available now, the in-hospital mortality did not strikingly differ between the two time periods, which means minimizing the in-hospital mortality of IE is still a long-term undertaking.

What we can't ignore is that 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[25]. Therefore, how to promote the medical capability for treating critically ill patients with IE is a question that deservers further study. This study focused on a single-center in a general teaching hospital without long-term follow-up. Most patients came from southern China, thus findings in this study may not be applicable to all populations. However, IE is an uncommon disease and few studies have been conducted in China. Our observations reflected a dynamic change of IE over a period of eighteen consecutive years with a relatively large sample size. The geographic variations observed in our study will be of important value to clinicians attempting to diagnose IE in our region.

In conclusion, patients with IE in recent years were relatively older and had a lower history of IVDU, which was probably responsible for fewer presentations of pulmonary embolism and renal failure, a lower positive rate of *Staphylococcus aureus* infection and fewer right heart vegetations. However, a greater incidence of ischemic stroke was observed possibly due to older age and unidentified factors. However, the in-hospital mortality rate was about the same for the two periods, which is an issue that deserves follow-up study.

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

Funding

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 Basic information of 313 IE patients

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

Variable	Total	Early-period group	Later-period group	*P*
	N=313	N=97	N=216	
Treatment regimen				
Antibiotic plus surgery	187 (59.7)	57 (58.8)	130 (60.2)	0.812
Improvement at discharge	177 (94.7)	52 (91.2)	125 (96.2)	0.305
Antibiotic only	126 (40.3)	40 (41.2)	86 (39.8)	0.812
Improvement at discharge	38 (30.2)	13 (32.5)	25 (29.1)	0.696
Worsening at discharge	98 (31.3)	32 (33.0)	66 (30.6)	0.668
Death	35 (11.2)	11 (11.3)	24 (11.1)	0.953
Acute heart failure	14 (4.5)	4 (4.1)	10 (4.6)	0.924
Cerebrovascular events	10 (3.2)	3 (3.1)	7 (3.2)	0.781
Septic shock and multiple organ failure	9 (2.9)	5 (5.2)	4 (1.9)	0.211
Others	2 (0.6)	1 (1.0)	1 (0.5)	0.575†

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

Figures

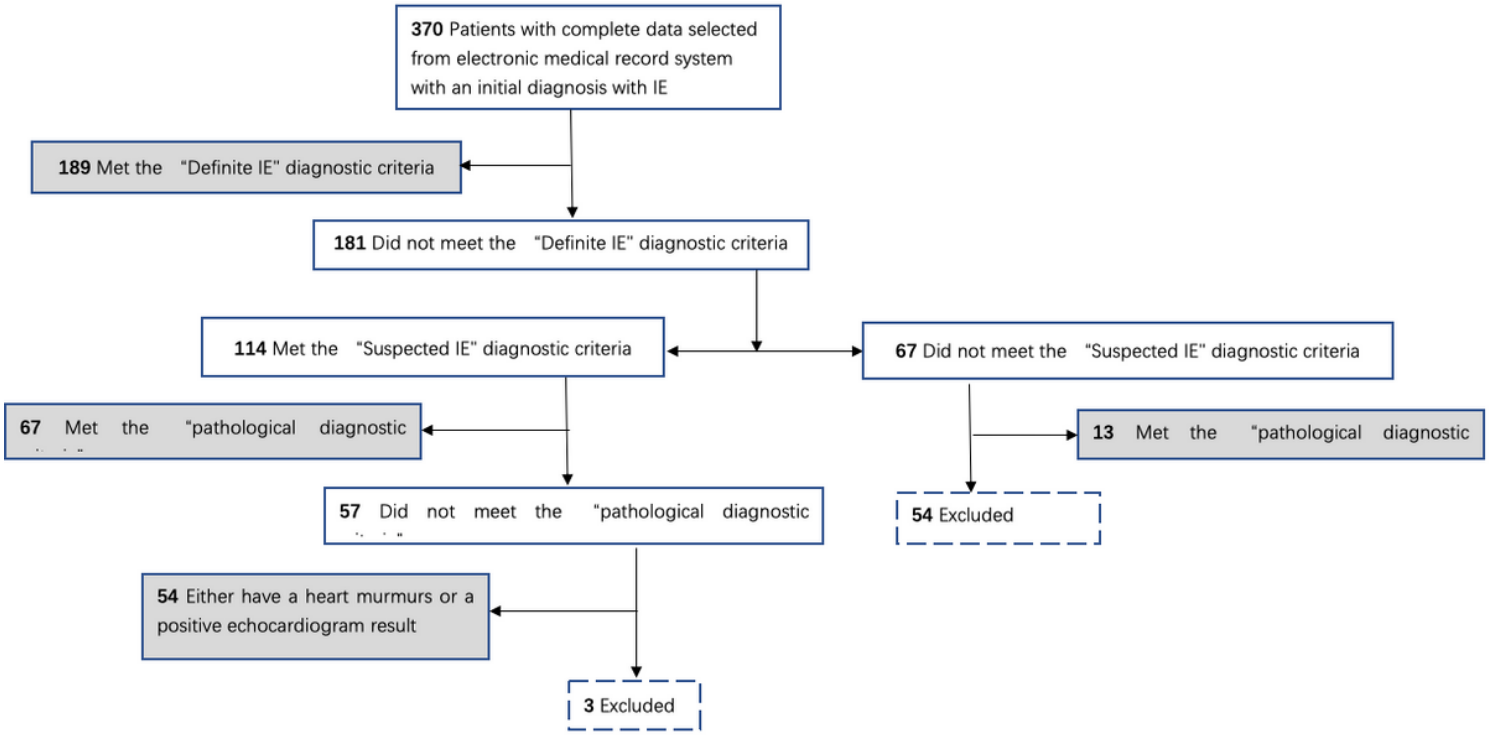

Figure 1