Epidemiology and risk factors of infective endocarditis in a tertiary hospital in China from 2007 to 2016

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Research

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Abstract

Background: To explore the trends in epidemiology and risk factors related to the prognosis of infective endocarditis in a teaching hospital over the past ten years. **Methods:** A retrospective cohort study was performed. A total of 407 consecutive patients were included. The clinical characteristics and risk factors related to the prognosis of infective endocarditis during this period were analyzed.

Results: A total of 407 patients with infective endocarditis were included, the average age was 48 ± 16 years old with an increasing trend and in-hospital mortality rate was 10.6% and one-year mortality rate was 12.2%. Among patients with underlying heart disease, congenital heart disease was the most common (25.8%), followed by rheumatic heart disease which showed a decreased trend during this period ($P < 0.001$). There were 222 (54.5%) positive blood cultures and streptococci (44.1%) was the main pathogens with an increasing trend. There were 403 patients (99%) with surgical indications, but only 234 patients (57.5%) received surgical treatment. Hemodialysis ($P = 0.041$, OR = 4.697, 95% CI 1.068-20.665), pulmonary hypertension ($P = 0.001$, OR = 5.308, 95% CI 2.034-13.852), Pitt score ≥ 4 ($P < 0.001$, OR = 28.5, 95% CI 5.5-148.1) and vegetation length ≥ 30 mm ($P = 0.011$, OR = 13.754, 95% CI 1.832-103.250) were independent risk factors for in-hospital mortality.

Conclusions: There was no significant change in the overall incidence of IE, the clinical features of IE have changed slightly during the past ten years. Streptococci IE was still the predominant. IE patients with hemodialysis, pulmonary hypertension, Pitt score ≥ 4 and vegetation length ≥ 30 mm had an worse in-hospital outcome.

Background

Infective endocarditis (IE) is an infectious disease involving the heart valve or endocardium caused by causative microorganisms. It is a severe disease with high morbidity and mortality [1]. Serious complications such as heart failure and cerebral embolism are common. In developed countries, the annual incidence is between 3 and 9 patients per 100,000 persons with a slight increase between 1970 and 2013 [1, 2]. Although the improvement of prevention, the progress of antibiotic therapy, the development of imaging technology and the intervention with surgery, the mortality is still 15–30% [3]. Over the past two decades, with the increase in life expectancy, the increased use of cardiac implant devices, and the frequency in invasive procedures, the epidemiology of IE in developed countries has changed significantly: older patients with IE gradually increased, prosthetic valve endocarditis (PVE) and IE associated with implanted devices increased, and Staphylococci has become the most predominated pathogen [4].

However, studies from developing countries such as Turkey showed a different epidemiological character [5]. In their study, although staphylococcal IE was increasing, streptococci was still the most predominant pathogen; rheumatic heart disease (RHD) and congenital heart disease (CHD) were still the most common underlying heart diseases, and the number of patients undergoing surgical treatment was

increasing[5, 6]. In this study, we analyzed the changes in clinical features of IE over the past 10 years to explore the trend of IE and problems existing on diagnosis and treatment in our region.

Methods

Patients

A retrospective, consecutive case-series analysis was organized and performed in the First Affiliated Hospital of Zhejiang University, Hangzhou, China. Patients with a clinical diagnosis of IE from January 1, 2007 to December 31, 2016 were reviewed. The Modified Duke criteria [1] was used to evaluate patients reviewed. Patients who were admitted to the hospital more than one time for the same pathogen during the study period were considered as one case.

Clinical parameters and study design

The data were retrieved from the Electronic Medical Record. The data included in the analysis were patient demographic information, underlying heart diseases, comorbidities, clinical manifestations, complications, causative microorganisms, echocardiographic demonstrations, treatments, and outcomes. The following data analysis strategies were conducted: (1) The changing trend of clinical characteristics in IE was analyzed with every two year time periods; (2) To explore the prognostic risk factors, the comparison between the survival group and the death group was conducted

Definition

Infective endocarditis was categorized based on disease types as native-valve endocarditis, prosthetic-valve endocarditis, and cardiac device-related endocarditis [1]. Embolism events included both central nervous system embolism and non-central nervous system embolism. Transthoracic echocardiogram (TTE) was performed routinely in all patients. Transesophageal echocardiogram (TEE) was used to detect cases with negative TTE results. Blood culture was performed in all the patients with aerobic, anaerobic and fungal blood cultures, but blood culture for the HACEK group (*Haemophilus spp*, *Aggregatibacter spp*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) and *anti-legionella*, *mycoplasma* and *bartonella* anti-body tests as well as PCR test were not performed when patients had negative blood culture results.

Statistical analysis

The trends in clinical characteristics was performed using the log-linear Poisson regression model. Univariate analysis was performed using the Pearson's χ^2 test or Fisher's exact tests as appropriate for categorical variables and the independent Student's t-test or the Rank sum test as appropriate for continuous variables. Categorical variables were expressed as frequencies and percentages of the specified group and continuous variables were reported as averages with standard deviations or medians and interquartile ranges. After univariate analysis, variables with $P < 0.05$ were included in backward

stepwise logistic regression to identify predictors for in-hospital mortality among IE patients. Odds ratios (OR) with 95% confidence interval (CI) were calculated in logistic regression. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 23 statistical software.

Results

Patient enrollment

In our study, there were 409 patients with IE and 2 patients whose blood culture results were unreachable were excluded. A total of 407 IE patients were included. There were 43 patients (10.6%) died during hospitalization and 46 died (12.2%) in the one-year follow-up.

The clinical characteristics of patient with IE

Among the 407 patients, 262 patients were male (64.6%). The average age was 48 ± 16 years old with an increasing trend during this period ($P = 0.001$) (**Table 1**). The annual incidence of IE were between 0.33 and 0.72 patients per 1000 admissions and the incidence was stable over this period (**Figure 1**).

There were 186 patients (45.7%) without underlying heart disease and the proportion increased over this time ($P = 0.044$). CHD was the most common underlying heart disease, accounting for 25.8% of all patients, and the proportion of RHD decreased yearly during this period ($P < 0.001$). Patients with degenerative valvular disease (DVD) accounted for 3.2% with a growing trend ($P = 0.001$). Native valve IE was still the most dominant, with 370 patients (90.9%) and the proportion increased ($P = 0.002$). Except for hypertension with a significant increase in the proportion ($P = 0.005$), the proportion of other comorbidities did not change significantly. There were 215 patients (52.8%) with heart failure and 125 patients (30.7%) with cerebral embolization. The proportion of cerebral embolism was significantly increased in our study ($P = 0.001$).

TEE was performed on 53 patients (13.0%) and 30 patients (7.4%) were diagnosed after TEE. The detection rate of vegetation was 86.7% with a significant growth trend ($P < 0.001$). There were 72 patients (17.7%) with valve perforation and 30 patients (7.4%) with perivalvular abscess. Left-side IE was the most common with 356 patients (87.5%). A single valve being affected was more common, with 295 patients (72.5%), among which the mitral valve was affected in 134 patients (32.9%) and the aortic valve was affected in 143 patients (35.1%).

Blood cultures were performed in all patients with IE. Two hundred and twenty two (54.5%) blood cultures had positive results. Patients with negative blood culture were diagnosed as definite IE by the following criteria: 173 patients had positive echocardiographic findings plus three minor criterias, and 12 patients were identified by positive histopathological findings. Streptococci was the main pathogen, accounting for 24.1% of positive results with an increasing trend, followed by staphylococci, accounting for 18.9%.

There were 40 patients (18.0%) of staphylococcus aureus IE, including 26 patients (11.7%) of methicillin-resistant staphylococcus aureus (MRSA) IE.

The risk factors for in-hospital mortality

Univariate analysis found that age, previous heart valve surgery, hemodialysis, hypertension, heart failure, cerebral embolism, cerebral hemorrhage, arrhythmia, hepatic insufficiency, renal insufficiency, pulmonary hypertension, prosthetic valve or pacemaker valve IE, *Staphylococcus aureus* infection, Pitt score ≥ 4 , surgical treatment were related to the in-hospital mortality (Table 2). Multi-factor analysis showed, Hemodialysis ($P = 0.041$, OR = 4.697, 95% CI 1.068-20.665), pulmonary hypertension ($P = 0.001$, OR = 5.308, 95% CI 2.034-13.852), Pitt score ≥ 4 ($P < 0.001$, OR = 28.5, 95% CI 5.5-148.1) and vegetation length ≥ 30 mm ($P = 0.011$, OR = 13.754, 95% CI 1.832-103.250) were independent risk factors for in-hospital mortality (Table 3).

Discussion

Over the past decades, the epidemiology of IE has changed due to changes in demographic characteristics and risk factors. Researches from developed countries showed that the incidence of IE had increased in the past decades [4]. Cresti et al [7] found the incidence was 4.6/100,000 person-years with a significant linear increase between 1998 and 2014. Keller et al [8] found that the incidence of IE in Germany was 11.6/100,000 person-years between 2005 and 2015 and the incidence increased continuously during the study period, especially in the last five years. However, in our study, we found that the incidence of IE was between 0.33 and 0.72 patients per 1000 admissions and the incidence remained stable during the period, which was lower in comparison with the developed countries (approximately 1-1.3 patients per 1000 hospital admissions) [4, 7]. The difference in incidence of IE from different studies may be related to the geographical location of the study, the time period selected, and the difference in diagnostic techniques of different institutions.

In our study, we found that the mean age at the time of IE episodes were younger than those reported from developed countries, although the mean age increased during this period. The proportion of old patients with IE increased gradually in our study period, and this shown the same trend as the developed countries [7, 9]. Erichsen et al [10] found that the incidence increased substantially for elderly patients between 1994 and 2011, with the highest incidence rate of 3.38 for patients more than 80 years old at IE onset. In Oliver et al's report [11], 49% of IE patients were over 65 years old and 11.2% were over 80 years old. The changes in the age of IE onset may owing to the aging population. And as a result of the older onset age, patients with IE in the latter part of the study period were more likely to have comorbidities compared with patients in the earlier part of the study period.

We found that CHD had become the most common underlying heart disease for patients with IE in our study. RHD was once the most common underlying heart disease in the 1990s according to Chao et al's report [12]. But the proportion of RHD gradually decreased in our study. The results from other medical institutions in China also found the same change on underlying heart disease in patients with IE [13].

Previous reports from developed countries also presented that the proportion of RHD had dropped obviously, and DVD, PVE and implantable electronic devices related IE had gradually increased and replaced RHD as the leading heart disease [1, 4, 8]. This difference may contributed to the large number of patients with CHD and the relative low proportion of patients with prior cardiac surgery. According to the published reports, the risk of developing into IE increased in patients with CHD [14–16]. Darren et al [16] found that the IE risk exceeded 100 times in patients with ACHD compared to that of the general population and 2.5 times that of children with CHD [16, 17]. The proportion of patients with CHD in our study was as high as 25.8%.

TEE was performed in only 13% patients with IE in our study, as most patients diagnosed after TTE did not perform TEE routinely. Based on a review of the literature published from China on IE, the rate was similarly but it approached to other studies in our region [13, 18, 19]. But this rate was significantly lower than that reported by other studies from developed countries with 74%-100% [20, 21]. However, according to the 2015 European Association of Cardiology guidelines on IE, for TTE positive patients, TEE should be performed to exclude perivalvular complications [1]. The low utilization rate of TEE could directly resulted in the low detection rate of perivalvular complications such as valvular perforation and perivalvular abscess in our study. They were very important data for the cardiac surgeon. Besides, this could cause the missed diagnoses of IE in patients with unobvious valvular lesions or with basic valvular lesions. This underlined that our research institution still needs to strengthen the learning of the value of TEE in IE diagnosis, strengthen the study of the latest IE guidelines and improve the use of TEE in the diagnoses of IE to reduce missed diagnoses.

The positive rate of blood culture in our study was lower compared with other studies from developed countries, where the rate of a positive blood culture varied from 83–96% [2, 8, 11, 22]. However, the positive culture rate was approximate to other studies from China varied from 38.5–70.1% [13, 18, 23]. This finding could be related to the use of antibiotics before blood culture, because in our study the proportion of patients with prior antibiotics use was as high as 81.7%. As a tertiary hospital, most patients in our hospital had been referred from other medical institutions. They usually had a history of antibiotic use prior to the blood cultures. Besides, the blood cultures of the HACEK group, serology tests for mycoplasma, bartonella, legionella and the polymerase chain reaction (PCR) were not performed in our hospital. All these factors resulted in the low microbiology detection rate. We suggested that patients with suspected bloodstream infection should receive blood cultures routinely before the use of antibiotics to rule out or confirm the diagnosis of bloodstream infection.

In our study, streptococci was the main pathogen accounting for 24.1%, followed by staphylococci accounting for 18.9%, which was the same as the report in the 1990s from China [12]. This was similar to other developing countries [5, 6] but different from developed countries [4]. For IE in developed countries, the proportion of staphylococci increased gradually and became the main pathogenic bacteria [4, 6]. The increase in staphylococcus IE was mainly due to the high incidence of intravenous drug addicts, hemodialysis patients and elderly patients with comorbidities [3, 4, 24]. However, in our study, the proportion of patients with intravenous drug addicts, hemodialysis patients and octogenarians was lower

compared with developed countries. Besides, streptococcus IE was the main for community origin IE according to the previous reports, and most of patients in our study were community origin IE [19].

According to published studies, older age, prosthetic valve IE, heart failure, septic shock staphylococcus aureus, and large vegetation were predictors of poor outcome in patients with IE [1, 4]. In our study, we also found that hemodialysis and pulmonary arterial hypertension were independent risk factors of in-hospital mortality. The risk of in-hospital mortality in patients with Hemodialysis increased by 4.697 times and in patients with pulmonary arterial hypertension, the risk of in-hospital mortality increased by 5.308 times.

There are several limitations in our study. First, as a retrospective study, there exists information bias, and we were unable to obtain information on patient exposure to dental procedures and the use of antibiotic prophylaxis. Second, the study used a single-center cohort in a referral teaching hospital with possible selection bias that could not represent the entire Chinese condition. Finally, as a nonrandomised study, there were associated limitations and selection bias affecting comparisons between the in-hospital outcomes. Therefore, we suggest multiple-center prospective cohort studies performed in our region.

Conclusions

In conclusion, this study is currently a large sample research in IE from our region. It presents the clinical features of IE in currently in our region that the age at the time of IE episodes has being older, congenital heart disease is the predominant cardiac disease and streptococci is still the predominant pathogen. Besides, it showed that patients with hemodialysis, pulmonary hypertension, Pitt score ≥ 4 and vegetation length ≥ 30 mm had an worse in-hospital outcome. Our results will have an important impact in the improvement in the diagnosis and treatment of IE in our region in the future.

Abbreviations

IE: infective endocarditis; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; SD: standard deviation IQR: interquartile range; OR: odds ratios; HR: hazard ratio; CI: confidence interval

Declarations

Ethics approval and consent to participate

Ethics approval for this study was submitted and approved through Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. The consent to participate is not applicable because the study design is a retrospective data collection. The Research Ethics Committee of the Hospital was responsible for administrative permissions to access the raw data.

Consent for publication

Not applicable.

Availability of data and materials

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

Conflicting of interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

ZZW designed the study and created study protocols, ZZW and YC performed the data collection, data analysis and drafts the manuscript. YHX supervised the study development, helped to review the manuscript and made critical revision to the paper. TTX TSN and QYS performed data collection and helped to review the manuscript. All authors read and approved the final manuscript.

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Tables

		Total n=407	2007- 2008 n=62	2009- 2010 n=63	2011- 2012 n=78	2013- 2014 n=89	2015-2016 n=114	P value
		262(64.4)	40(64.5)	42(66.7)	53(67.9)	56(62.9)	71(61.7)	.513
SD		48±16	45±15	42±15	47±16	50±16	52±16	.001
ities								
on		82(20.1)	9(14.5)	9(14.3)	11(14.1)	20(22.5)	33(28.7)	.005
ellitus		37(9.1)	3(4.8)	5(7.9)	6(7.7)	8(9.0)	15(13.0)	.078
an disease		23(5.7)¶	3(4.8)	3(4.8)	2(2.6)	6(6.7)	9(7.8)	.260
		12(2.9)	2(3.2)	2(3.2)	4(5.1)	2(2.2)	2(1.7)	.474
ng heart disease		186(45.7)	18(29.0)	29(46.0)	42(53.8)	40(44.9)	57(49.6)	.044
heart disease		221(54.3)	44(71.0)	34(54.0)	36(46.2)	49(55.1)	58(50.4)	.044
heart disease		105(25.8)	17(27.4)	16(25.4)	18(23.17)	26(29.2)	28(24.3)	.870
heart disease		69(17.0)	22(35.5)	14(22.2)	12(15.4)	6(6.7)	15(13.0)	¶.001
rdiac surgery		44(10.8)	11(17.7)	6(9.5)	6(7.7)	15(16.9)	6(5.2)	.086
re heart disease		13(3.2)	0	0	2(2.6)	2(2.2)	9(7.8)	.001
y, mean±SD		25±22	31±31	32±25	23±17	23±24	21±15	.001
		13(4-35)	17(7-48)	14(6-30)	15(4-40)	9(3-50)	15(4-31)	.542
before echocardiography								
),days								
symptoms		25(12-62)	26(12-68)	24(9-42)	25(14-62)	28(10-75)	26(13-62)	.434
mosis¶								
),days								
ptic use		321(81.7)	48(81.4)	58(92.1)	65(90.3)	76(85.4)	74(67.3)	.001
; drug abuse		3(0.7)	1(1.6)	1(1.6)	0	0	1(0.9)	.556
und signs								
		365(89.7)	57(91.9)	57(90.5)	70(89.7)	83(93.3)	98(85.2)	.233
		222(54.5)	38(61.3)	43(68.3)	43(55.1)	58(65.2)	40(38.4)	¶.001
a		7(1.7)	2(3.2)	0	3(3.8)	2(2.2)	0	.288
ions or nailbed bleeding		4(0.9)	1(1.6)	3(4.8)	0	0	0	.06
		53(13.0)	3(4.8)	4(6.3)	5(6.4)	8(9.0)	32(27.8)	¶.001
site								.342
		356(87.5)	53(85.8)	54(85.7)	67(85.9)	79(88.8)	103¶89.6¶	
		31(7.6)	7(11.3)	3(4.8)	8(10.3)	4(4.5)	9(7.8)	
-side		20(4.9)	2(3.2)	6(9.5)	3(3.8)	6(6.7)	3(2.6)	
lve								¶.05
		295(72.5)	38(61.3)	46(73.0)	55(70.5)	58(65.2)	98(85.2)	.002
,		134(32.9)	16(25.8)	20(31.7)	24(30.8)	30(33.7)	44(38.3)	
,		143(35.1)	18(29.0)	23(36.5)	25(32.1)	27(30.3)	50(43.5)	
n(%)		79(19.4)	13(21.0)	15(23.8)	13(16.7)	24(27.0)	14(12.2)	
l or arterial intima		33(8.1)	11(17.7)	2(3.2)	10(12.8)	7(7.9)	3(2.6)	
IE								
e IE		370(90.9)	50(80.6)	58(92.1)	72(92.3)	77(86.5)	113(98.3)	.002
valve IE or pacemaker valve IE		37(9.1)	12(19.3)	5(7.9)	6(7.7)	12(13.5)	2(1.7)	.002
ations								
ents		125(30.7)	14(22.6)	16(25.4)	16(20.5)	34(38.2)	45(39.1)	.003
nbolism		74(18.2)	6(9.7)	7(11.1)	12(15.4)	18(20.2)	31(27.0)	.001
e		215(52.8)	31(50.0)	31(49.2)	43(55.1)	51(57.3)	59(51.3)	.661
		353(86.7)	44(71.0)	56(88.9)	62(79.5)	83(93.3)	108(93.9)	¶.001
extent								
		90(22.1)	9(14.5)	12(19.0)	16(20.5)	2(23.6)	32(27.8)	
m		197(48.4)	25(40.3)	31(49.2)	31(39.7)	52(58.4)	58(50.4)	
mm		51(12.5)	8(12.9)	10(15.9)	14(17.9)	6(6.7)	13(11.3)	
		12(2.9)	2(3.2)	1(1.6)	1			

TEE: Transesophageal echocardiography

Table2 Risk factors of in-hospital outcome in patients with infective endocarditis[univariate analysis]

Variable, n (%)	In-hospital outcome		P value
	Survival n=364	Death n=43	
Age ,mean $\pm$ SD	48 $\pm$ 16	53 $\pm$ 16	.047
Man	237(65.1)	25(58.1)	.367
Underlying heart disease	176(48.4)	25(58.1)	.225
Rheumatic heart disease	54(14.8)	4(9.3)	.051
Congenital heart disease	70(19.2)	8(18.6)	.921
Previous cardiac surgery	27(7.4)	10(23.3)	.001
Degenerative heart disease	12(3.3)	1(2.3)	.075
Others	26(7.1)	2(4.7)	.075
Comorbidities			
Chronic obstructive pulmonary disease	5(1.4)	1(2.3)	.491
Cancer	11(3.0)	1(2.3)	.05
Hemodialysis	9(2.5)	5(11.6)	.002
Liver cirrhosis	4(1.1)	0	.05
Hypertension	68(18.7)	14(32.6)	.032
Diabetes mellitus	32(8.8)	5(11.6)	.541
Complications			
Heart failure	179(49.2)	36(83.7)	.001
Intracranial infection	15(4.1)	2(4.7)	.698
Cerebral embolism	55(15.1)	19(44.2)	.001
Cerebral hemorrhage	16(4.4)	7(16.3)	.001
Arrhythmia	65(17.9)	15(34.9)	.008
Hepatic insufficiency	57(15.7)	15(34.9)	.002
Renal insufficiency	60(16.5)	21(48.8)	.001
Pulmonary arterial hypertension	92(25.6)	24(57.1)	.001
Valvular perforation	64(17.7)	8(18.6)	.881
Perivalvular abscess	26(7.2)	4(9.3)	.544
Vegetation length			.001
$\leq$ 10mm	137(37.6)	10(23.3)	
10mm-20mm	177(48.6)	20(46.5)	
$\geq$ 20mm $\leq$ 30mm	46(12.6)	5(11.6)	
$\geq$ 30mm	4(1.1)	8(18.6)	
Vegetation extent	142(39.0)	16(37.2)	.819
IE type			.004
Native valve IE	337(92.6)	33(76.7)	
Prosthetic valve IE or pacemaker valve IE	27(7.4)	10(23.3)	.001
Prior antibiotic use	291(80.2)	30(69.8)	.204
Causative organism			.033
Streptococci	75(20.6)	3(7.0)	
Staphylococci	53(14.6)	12(27.9)	
Staphylococcus aureus	20(5.5)	8(18.6)	.001
Pitt score			.001
$\leq$ 4	359(98.6)	23(53.5)	
$\geq$ 4	5(1.4)	20(46.5)	
Surgical treatment	220(60.4)	14(32.6)	.001

Table3 Risk factors of in-hospital outcome in patients with infective endocarditis[multivariate analysis]

Variable	P value	OR	95%CI
Male	.413		
Cerebral embolism	.137		
Hemodialysis	.041	4.697	1.068-20.665
Pulmonary arterial hypertension	.001	5.308	2.034-13.852
Pitt score ≥ 4	.000	111.617	28.255-440.934
Vegetation length ≥ 30 mm	.011	13.754	1.832-103.250
Prosthetic valve IE or pacemaker	.064		
Surgical treatment	.325		

Figures

Figure 1

Incidence of infective endocarditis from 2007 to 2016 in hospitalized patients (Linear regression showed $P=0.168$)