Risk factors and survival analysis of haemodialysis complicated with infective endocarditis

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Abstract. The clinical features and risk factors for survival time were analysed in haemodialysis patients complicated with infective endocarditis. A total of 101 infective endocarditis (IE) patients treated at Hangzhou First People's Hospital, from January 1, 2012, to April 1, 2022, were included in the present study. Baseline demographic data and laboratory data were collected for statistical analysis of risk factors and survival time in the IE with haemodialysis group (HD-IE group, n=15) and the IE without haemodialysis group (NHD-IE group, n=86). Haemoglobin, red blood cells, C-reactive protein, procalcitonin, serum albumin, diabetes, invasive procedures, positive blood bacteria culture, heart valve calcification ratio, and left ventricular ejection fraction level were risk factors for infective endocarditis complicated with haemodialysis (P<0.05). Compared with the NHD-IE group, the HD-IE group had an obviously increased risk of mortality (χ^2=6.323, P=0.012). The univariate Cox regression analysis showed that age, haemoglobin, red blood cells, serum albumin, left ventricular ejection score, longest vegetation diameter, combined hypotension and diabetes were risk factors for death; furthermore, multivariate Cox regression showed that age (HR=1.187, P=0.015), combined hypotension (HR=0.921, P=0.025) and the longest vegetation diameter (HR=9.191, P=0.004) were independent risk factors affecting the survival of patients. Collectively, the present study revealed that the mortality rate of HD-IE patients was higher than that of NHD-IE patients. Older age, hypotension, and the longest vegetation diameter were independent risk factors affecting the survival of patients. For HD-IE patients, active and effective antibiotic treatment or surgical treatment should be strongly recommended.

Introduction

Improving the survival prognosis of patients with end-stage renal disease (ESRD) is the ultimate goal of renal replacement therapy, and it is also an important criterion for determining the clinical efficacy of dialysis mode. Although haemodialysis treatment has made great progress, the survival prognosis of maintenance haemodialysis patients is still not optimistic. Previous studies reported that the annual mortality rate of haemodialysis patients in Japan is 9.8-10.2% (1), and the annual mortality rate of dialysis patients is 23.6% in the United States (2). The mortality rate of dialysis patients in China is 20% (3). Cardiovascular complications are the leading cause of death in end-stage renal disease. With the continuous deterioration of renal function, the incidence of cardiovascular complications in patients with end-stage renal disease is markedly increased. Deaths caused by cerebrovascular disease (CVD) account for 50% of the total mortality of end-stage renal disease (4). Infective endocarditis (IE) is the main complication of ESRD-related CVD.

IE with acute injury of the heart valve or ventricular wall lining is caused by invasion of the endocardium by bacteria, fungi, and other pathogenic microorganisms. Haemodialysis patients are more likely to develop IE than nonhaemodialysis patients. The incidence of haemodialysis complicated with IE is 2-5% (5), and the mortality rate of haemodialysis patients with IE is extremely high.

The aim of the present retrospective study was to explore the risk factors and survival prognosis of haemodialysis patients with IE to further improve the quality of treatment and reduce mortality.

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Patients and methods

Patients. A total of 101 IE patients admitted to Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine (Hangzhou, China), from January 1, 2012, to April 1, 2022, were retrospectively included (50 males and 51 females; their age was 57.9±18.1 years old). The present study was performed according to the Declaration of Helsinki and approved by the local ethics board of Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine. Individual patient consents were waived on the condition that all patients were deidentified before analysis since this study was a retrospective analysis.

The inclusion criteria were as follows: i) The age of the patients was ≥18 years old; ii) the echocardiography of the heart showed the formation of valvular vegetations; and iii) the diagnosis met the modified Duke diagnostic criteria (6).

The exclusion criteria were as follows: i) Patients with mental disorders who could not cooperate and ii) patients who were identified as having an infection in other parts of the body.

Groups. In the IE with haemodialysis (HD-IE) group, 15 IE patients were diagnosed with end-stage renal disease and had been on haemodialysis for >3 months. Among them, the primary disease was chronic glomerulonephritis in seven cases, diabetic nephropathy in six cases, hypertensive nephropathy in one case, and amyloid nephropathy in one case. Vascular access was used in eight patients with autologous arteriovenous fistula. A total of seven patients had long-term indwelling subcutaneous tunnel polyester sleeve catheters, and the frequency of dialysis was three times a week. The IE without haemodialysis (NHD-IE) group consisted of 86 IE patients with normal renal function.

Clinical data. The demographics, primary disease, and clinical indicators of the two groups were collected and compared. The clinical indicators included blood leukocytes, haemoglobin, blood albumin, high-sensitivity C-reactive protein (hs-CRP), triglycerides, high-density lipoprotein cholesterol (HDL-C), total cholesterol, blood leukocytes, helper T cells CD4, procalcitonin (PCT), and echocardiography.

Follow-up. The follow-up time was from January 1, 2012 to April 1, 2022. Patient survival was defined as the end event of death, and time was defined as the number of months from the diagnosis of IE to the death of the patient.

Statistical analysis. SPSS 20.0 software (IBM Corp.) was used for statistical analysis. The measurement data of continuous variables conforming to a normal distribution are expressed as the mean ± SD, and the comparison between groups was performed using one-way ANOVA followed by Tukey's post hoc test. Continuous variables with non-normal distribution data are expressed as M (1/4, 3/4). The independent samples t-test was used for normally distributed variables, and the χ^2 test was used for categorical variables; the nonparametric rank sum test was used to compare variables that did not conform to the normal distribution. Prognostic survival analysis was performed using the Kaplan-Meier method. A Kaplan-Meier survival analysis was used to evaluate the survival rate of the HD-IE group and NHD-IE group using the Breslow test. A Cox regression model was used to analyse the independent risk factors for IE, and the relative risk was described by hazard ratios (HRs) and 95% confidence intervals (CIs). P<0.05 was considered to indicate a statistically significant difference.

Results

General information comparison. The general data of the two groups are compared in Table I. There were significant differences in the levels of haemoglobin, red blood cells, CRP, PCT, and serum albumin between the two groups at admission (P<0.05). The levels of haemoglobin, red blood cells, and serum albumin in the HD-IE group were generally lower than those in the NHD-IE group, while CRP and PCT were significantly higher than those in the NHD-IE group. The differences in the positive rates of bacterial culture, diabetes, and invasive procedures were significant (P<0.05), while the differences in the levels of triglycerides, HDL-C, triglyceride (TG)/HDL-C and total cholesterol were not (P>0.05).

As revealed in Fig. 1, aortic valve injury was most common in IE patients, followed by mitral valve, tricuspid valve, and pulmonary valve injury. The involvement rates of the aortic valve, mitral valve and right atrium in HD-IE were 46.7, 46.7 and 6.6%, respectively. The aortic and mitral valve involvement rates in NHD-IE were 47.7 and 30.2%, respectively. As shown in Table I, there were no significant differences in the diameter of the longest vegetation of the heart valve, the degree of heart valve regurgitation, whether the heart valve was complicated by abscess perforation, whether it was complicated by hypotension, or whether it was complicated by underlying cardiovascular disease between the two groups (P>0.05). The proportion of heart valve calcification and the level of left ventricular ejection fraction were significant (P<0.05). The proportion of heart valve calcification in the HD-IE group was significantly higher than that in the NHD-IE group, and the level of left ventricular ejection fraction was lower than that in the NHD-IE group.

Aetiology. As revealed in Table I, the positive rate of bacterial culture in the NHD-IE group was 24.4%, and that in the HD-IE group was 60%. *Staphylococcus aureus* (*S. aureus*) is relatively common in the general population (7); however, the common pathogen in the NHD-IE group was *Streptococcus*, while the common pathogen in the HD-IE group was *S. aureus* (Fig. 2).

Prognosis analysis. Patients were followed up until death or until the end of observation on April 1, 2022. The survival rate of the two groups was assessed by a Kaplan-Meier survival analysis. The results of the Breslow test showed that the difference in the survival rate between the two groups was significant (χ^2=6.323, P=0.012). The results revealed that NHD-IE had a longer survival time than HD-IE, and HD-IE had a higher early mortality rate, as shown in Fig. 3. The Cox proportional hazards model was used to explore the factors influencing survival prognosis. The univariate Cox regression analysis showed that age, haemoglobin, red blood cells, blood albumin, left ventricular ejection fraction, longest vegetation

Table I. Comparison of baseline clinical data of patients with NHD-IE and HD-IE.

Variables	NHD-IE	HD-IE	P-value
Sex (M/F)	43/43	7/8	0.812
Age (years)	61.5 (39.75, 71.00)	70 (53.00, 75.00)	0.145
WBC ($\times 10^9$/l)	8.25 (6.00, 12.27)	9.56 (6.40, 15.39)	0.420
RBC (g/l)	108.73±21.05	77.27±17.86	<0.001
Hb (g/l)	3.76 (3.28, 4.10)	2.45 (2.17, 3.18)	<0.001
hs-CRP (mg/l)	58.35 (21.25, 94.00)	132.60 (26.00, 160.00)	0.009
PCT (ng/ml)	0.19 (0.08, 1.01)	3.31 (0.78, 13.72)	<0.001
Alb (g/l)	33.25±4.84	27.89±3.70	<0.001
TG (mmol/l)	1.11 (0.87, 1.49)	1.31 (1.10, 1.84)	0.162
TC (mmol/l)	3.59 (3.04, 4.22)	3.31 (2.89, 3.84)	0.207
HDL-C (mmol/l)	0.92 (0.70, 1.18)	0.89 (0.75, 0.99)	0.625
TG/HDL-C (mmol/l)	1.29 (0.88, 1.85)	1.57 (1.17, 2.06)	0.139
Combined hypotension (yes/no)	13/73	4/11	0.466
Combined diabetes (yes/no)	10/76	7/8	0.003
Invasive surgery (yes/no)	26/60	10/5	0.007
Paravalvular complications			
Perforation (yes/no)	15/71	1/14	0.502
Abscess (yes/no)	2/84	2/13	0.194
New moderate or severe regurgitation	64/22	11/3	0.741
Calcification (yes/no)	15/71	7/8	0.028
Concomitant heart disease (yes/no)	42/44	7/8	0.877
Vegetation size (mm)	0.88 (0.50, 1.20)	1.20 (0.55, 1.55)	0.203
EF	64.43±7349	57.99±9.408	0.018
Positive blood culture	21/65	9/6	0.013
Cardiac surgery performed (yes/no)	21/65	1/14	0.231

NHD-IE, infective endocarditis without haemodialysis; HD-IE, infective endocarditis with haemodialysis; M/F, male/female; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; hs-CRP, hypersensitive-C-reactive-protein; PCT, procalcitonin; Alb, albumin; TG, triglyceride; TC, serum total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG/HDL-C, triglyceride/high density lipoprotein cholesterol; EF, ejection fraction.

diameter and comorbid diabetes were the factors influencing mortality. Furthermore, multivariate Cox regression showed that age (HR=1.187, P=0.015), ejection fraction (HR=0.921, P=0.025), and the longest vegetation diameter (HR=9.191, P=0.004) were the main independent risk factors affecting the survival of patients, as revealed in Table II.

Discussion

Cardiovascular disease is the main complication and the leading cause of mortality in patients with end-stage renal disease. Among them, IE complicated with haemodialysis exhibits higher mortality than IE without haemodialysis. Patients with end-stage renal disease have a higher risk of IE than the general population due to their low immunity, multiorgan failure and a variety of underlying diseases, poor resistance to viruses or bacteria, and weakened stress responses. There is decreased erythropoietin production, a shortened erythropoiesis cycle, and insufficient clearance of accumulated toxins in the body to suppress bone marrow, resulting in different degrees of renal anaemia (8). At the same

time, combined with insufficient protein intake, digestive tract malabsorption and disease consumption, it is very easy to develop hypoproteinemia, which leads to further reduction of immune function and aggravates the incidence of infection (9,10). In the present study, the levels of haemoglobin, red blood cells, and albumin in the HD-IE group were lower than those in the NHD-IE group. Therefore, it is necessary to consider the malnutrition status of haemodialysis patients, prevent renal anaemia, and increase the intake of high-quality protein to improve immune function and prevent infection. Fever is the first symptom of IE, but echocardiography remains the main method for the imaging diagnosis of IE. Some patients need multiple echocardiography and transesophageal echocardiography to diagnose IE. In particular, experienced echocardiologists are particularly important for the diagnosis of IE. The present study did not analyse the differences in initial symptoms between the two groups, such as whether there was a difference in the type of fever in the two groups. This will be the direction of our future research.

Diabetic nephropathy accounts for a high proportion of end-stage renal disease in China. Hyperglycaemia causes
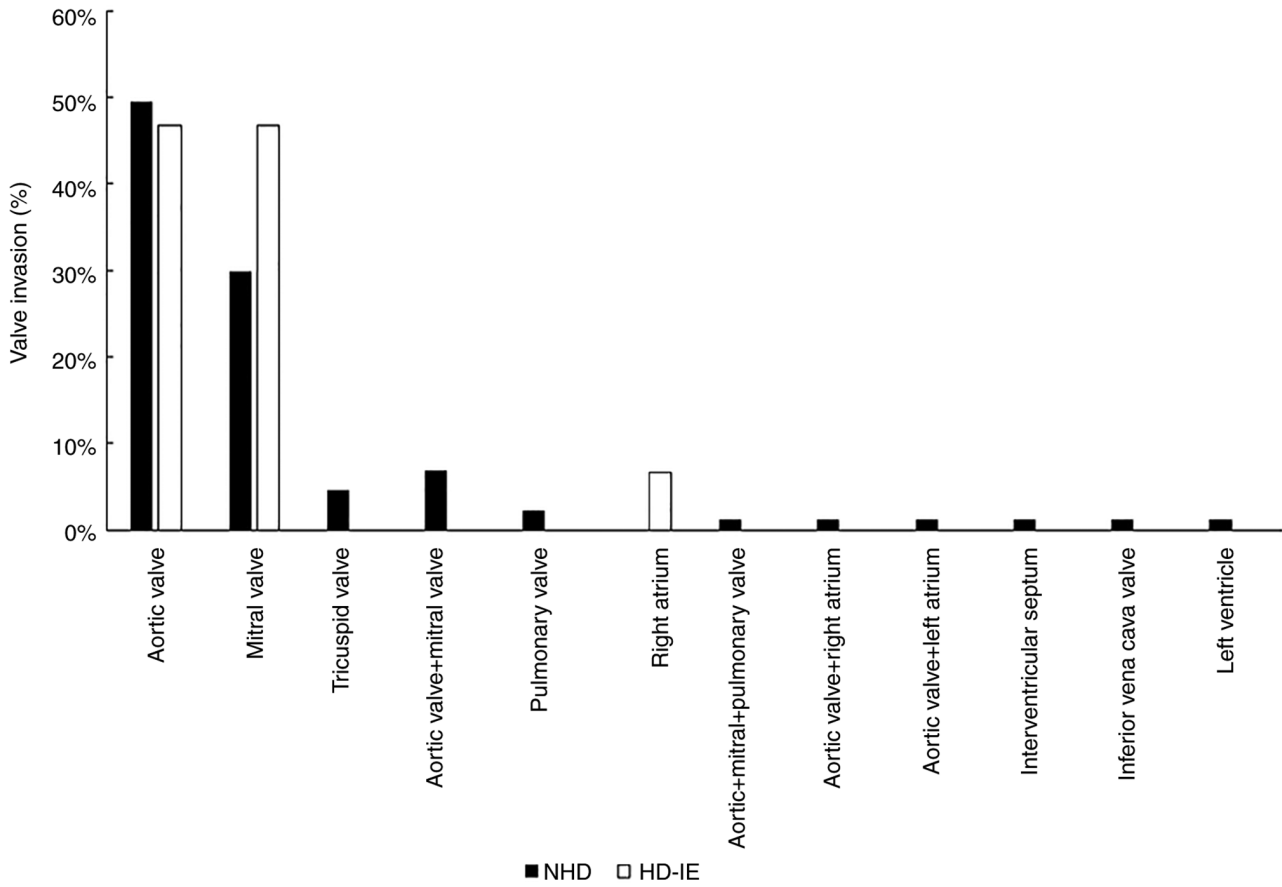
Figure 1. Valve involvement in IE patients. Injury of the aortic valve was most common in IE patients, followed by injury of the mitral valve, tricuspid valve, and pulmonary valve. IE, infective endocarditis.
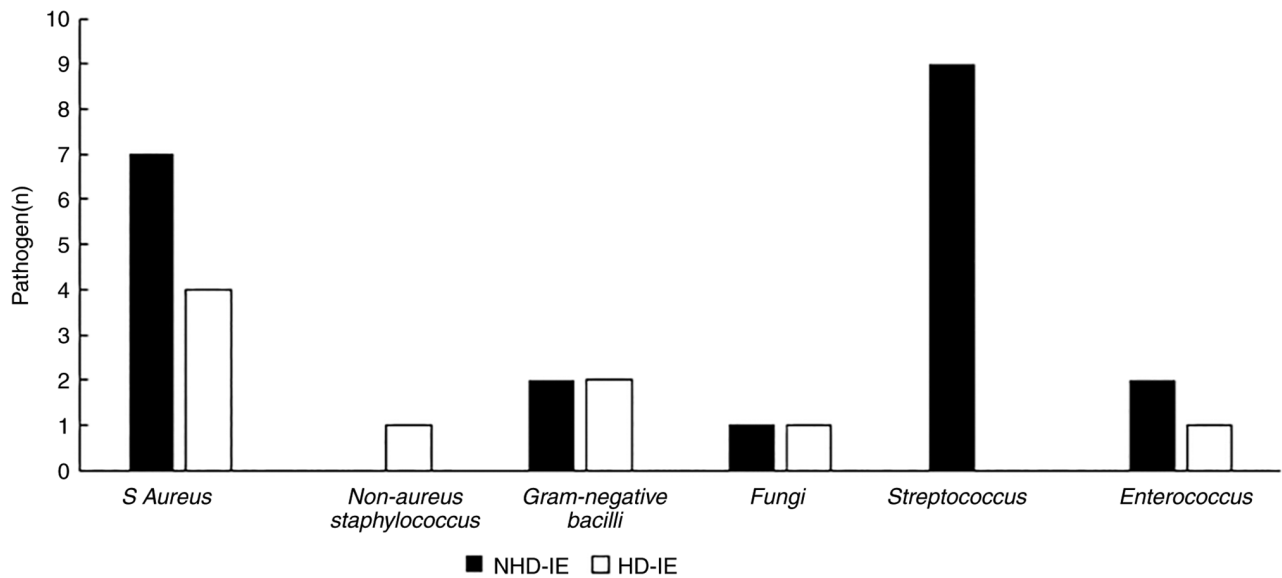

Figure 2. Pathogens in the HD-IE and NHD-IE groups. In the general population, *S. aureus* is relatively common. In the NHD-IE group, the most common pathogen was revealed to be *Streptococcus*. In the HD-IE group, the most common pathogen was *S. aureus*. HD-IE, infective endocarditis with haemodialysis; NHD-IE, infective endocarditis without haemodialysis; *S. aureus*, *Staphylococcus aureus*.

changes in plasma osmotic pressure, inhibits the phagocytic ability of immune cells, and inhibits leukocyte mobilization during ketosis; a high-glucose environment is conducive to the growth and reproduction of pathogens such as bacteria

and fungi (10-12). In the present study, the proportion of patients with diabetes mellitus in the HD-IE group was higher than that in the NHD-IE group, resulting in a higher risk of IE. In the HD-IE group, eight patients had autologous

Table II. Independent risk factors for mortality in NHD-IE and HD-IE patients (Cox regression analysis).

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Sex (M/F)	1.139	(0.383, 3.390)	0.815			
Age (years)	1.039	(0.998, 1.081)	0.06	1.187	(1.034, 1.363)	0.015
WBC (x10^9/l)	0.994	(0.953, 1.037)	0.78			
Hb (g/l)	0.97	(0.947, 0.995)	0.017	0.994	(0.994, 1.0466)	0.818
RBC (g/l)	0.479	(0.248, 0.925)	0.028	1.054	(0.884, 1.258)	0.557
hs-CRP (mg/l)	1.006	(0.997, 1.014)	0.183			
PCT (ng/ml)	1.027	(0.984, 1.073)	0.225			
Alb (g/l)	0.864	(0.772, 0.967)	0.011	0.892	(0.665, 1.196)	0.444
TG/HDL-C (mmol/l)	1.268	(0.762, 2.110)	0.36			
EF	0.969	(0.947, 0.992)	0.008	0.921	(0.856, 0990)	0.025
Vegetation size (mm)	2.083	(1.315, 3.299)	0.002	9.191	(1.966, 43.322)	0.004
Combined diabetes (yes/no)	3.246	(1.061, 9.927)	0.039	0.04	(0.001, 2.13)	0.112
Invasive surgery (yes/no)	1.128	(0.369, 3.447)	0.883			
Perforation (yes/no)	0.969	(0.215, 4.37)	0.967			
Abscess (yes/no)	2.113	(0.274, 16.279)	0.473			
New moderate or severe regurgitation	1.380	(0.425, 4.481)	0.592			
Calcification (yes/no)	1.598	(0.492, 5.191)	0.435			
Cardiac surgery performed (yes/no)	30.032	(0.117, 7737.065)	0.23			

arteriovenous fistula for vascular access, and 7 patients had long-term indwelling subcutaneous tunnel polyester sleeve catheters. Previous reports have noted that subcutaneous tunnel polyester sheath catheters are a risk factor for HD-IE because patients with long-term indwelling subcutaneous tunnel polyester sheath catheters have long-term contact with the wall of the haemodialysis catheter during dialysis, forming a layer of plasma protein membrane analogues. Known as plasma protein biofilms, plasma protein biofilms provide nutrients for bacterial aggregation, adhesion, colonization, and proliferation (13,14). Considering the increased risk of infection/bacteremia, infection-related hospitalizations and adverse consequences with long-term indwelling subcutaneous tunnel polyester sleeve catheters, experts suggest that most HD patients starting dialysis with long-term indwelling subcutaneous tunnel polyester sleeve catheters should convert to an arteriovenous fistula (15). However, it has been revealed that IE can also occur in patients with arteriovenous fistula, which is inconsistent with another previous report (16). The possible reasons for this could be that with the popularity of arteriovenous fistula, the utilization rate of arteriovenous fistula is increasing, and repeated skin puncture will increase the risk of bacterial infection. In addition, gram-positive bacteria (such as the *S. aureus* commonly present on the surface of medical staff and patients) more easily colonize and multiply on the skin surface to form infections (17). This is consistent with the findings of the present study, which revealed that *S. aureus* was a common pathogen in the HD-IE group. This suggests that the practice of handwashing, compliance with aseptic surgery procedures, publicity of surgery norms, and haemodialysis surgery training for medical staff before surgery, should be strengthened to reduce the risk of infection. As the sample size of present study was small, further study with a large multi-center sample size should be performed.

Compared with the general population, haemodialysis patients are more likely to develop vascular and valve calcification. Calcification is common in haemodialysis patients, and calcification-stimulating factors such as advanced age, high blood calcium, high intact PTH, inflammatory factors, oxidative stress, uraemic toxins, and glycation end products increase; meanwhile, calcification-inhibiting factors decrease, and calcification-stimulating factors and calcification inhibitors become imbalanced. Thus, supersaturated calcium and phosphorus in serum are deposited in blood vessels and valves. Mature vascular smooth muscle cells, mesangial progenitor cells in heart valves and cells with calcification tendency in blood circulation undergo apoptosis or transdifferentiation to become osteoblast-like cells, which in turn produce valve calcification (18,19). In the present study, the proportion of valve calcification in HD-IE patients was higher than that in NHD-IE patients. Therefore, for maintenance haemodialysis patients, vascular and valve calcification should be verified as soon as possible in order for effective intervention measures to be taken in time. In addition, the present study determined that the most common IE in haemodialysis patients is the left heart system and not the right heart system. There is no definite conclusion as to why IE is more likely to involve the left heart system. It may be related to intracardiac pressure (20).

In summary, compared with the general population, the possible causes of IE in haemodialysis patients include low immunity, malnutrition, diabetes and valve calcification. However, due to the limited sample size, the present study did not conduct in-depth analysis on etiology. In future studies, the sample size will be expanded to further analyse whether, for
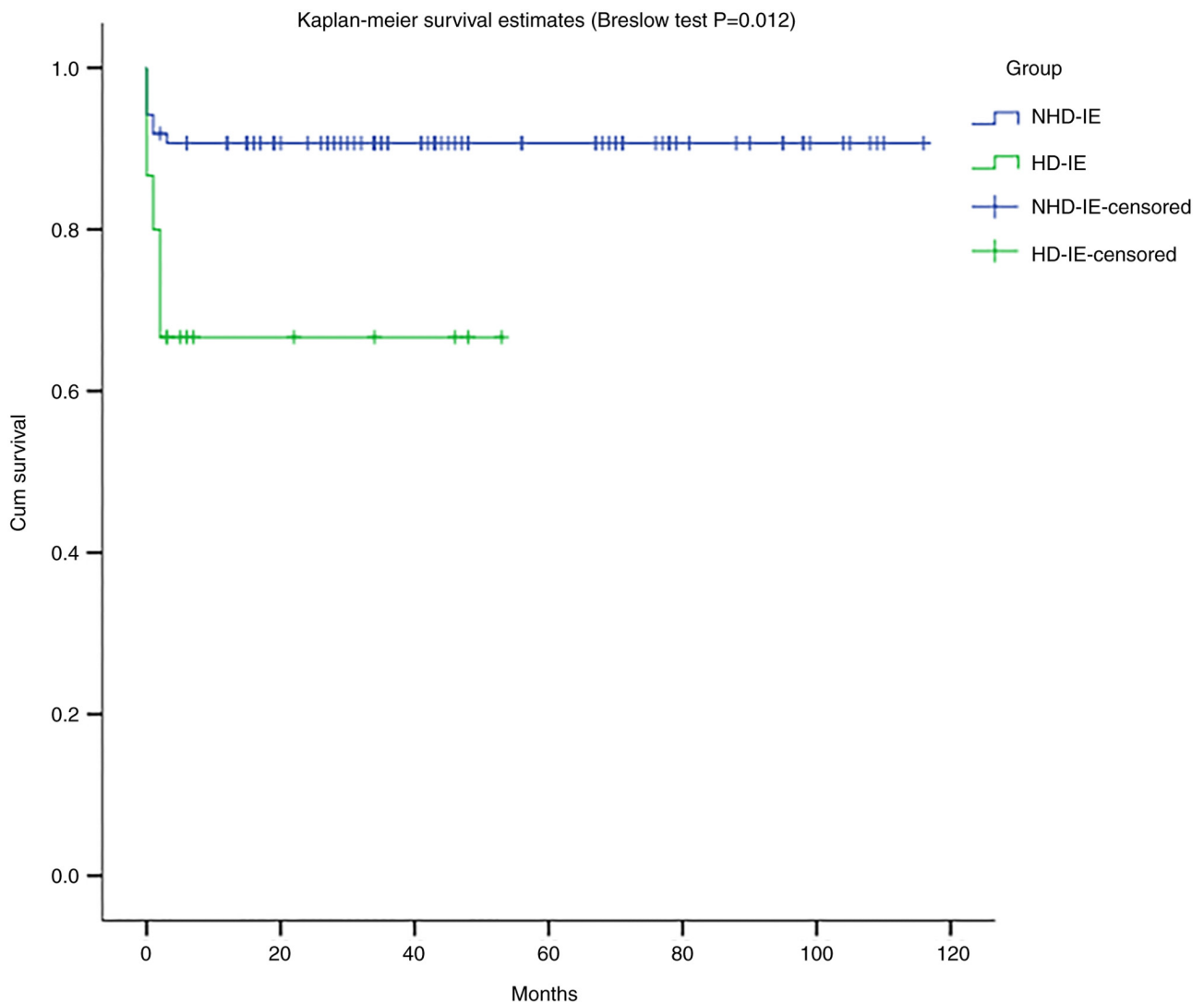
Figure 3. Kaplan-Meier survival estimates. The results of the Breslow test showed that the difference in the survival rate between the two groups was significant (χ^2=6.323, P=0.012). The results revealed that the NHD-IE group had a longer survival time than the HD-IE group, and HD-IE exhibited a higher early mortality rate. HD-IE, infective endocarditis with haemodialysis; NHD-IE, infective endocarditis without haemodialysis.

example, long-term indwelling subcutaneous tunnel polyester sleeve catheters will increase the risk of infection, especially since femoral vein catheterization is close to the perineum region. The influence of different types of vascular access on IE or the influence of catheter indentation time on IE will also be further explored.

Haemodialysis patients complicated with IE have a high mortality rate, and this is considered to be related to patients with end-stage renal disease complicated by multiple diseases, haemodynamic changes, autoimmune dysfunction, and a microinflammatory state (16,21). Raza *et al* (22) reported that the in-hospital mortality of HD-IE patients was 2.6 times that of ordinary patients. Ramos-Martinez *et al* (23) reported that the in-hospital mortality rate of HD-IE patients was 41%, and the 1-year mortality rate was as high as 56%. The present study suggests that HD-IE patients have a lower survival rate and shorter survival time than NHD-IE patients, which is consistent with a previous report (24). In terms of treatment, antibiotic therapy is the basic means of IE, followed by surgical treatment. HD-IE patients are considered to be

a high-risk population due to the combination of multiple diseases and low autoimmunity (5). Regarding the surgical rate, only one HD-IE patient in the present study received surgical treatment, while the rest of the patients selected conservative treatment. According to the IE management guidelines of the European Society of Cardiology Annual Meeting in 2015, the necessity of antibiotics and early surgical treatment of IE was emphasized (25). After the diagnosis of IE, a multidisciplinary treatment team should be quickly formed. In the present study, all cases received anti-infective therapy according to IE management guidelines of the Annual Meeting of the European Society of Cardiology, and the course of treatment was 4-6 weeks. Antibiotics according to drug sensitivity were selected; for staphylococcal endocarditis, in which pathogen drug sensitivity shows methicillin-sensitive *Staphylococcus*, benzoxicillin is the first choice; for streptococcal endocarditis, penicillin is preferred for sensitive strains; for *Enterococcus faecium* endocarditis, penicillin in combination with amoxicillin or ampicillin in combination with aminoglycoside antibiotics are preferred; for aerobic

gram-negative bacterial endocarditis, piperacillin combined with gentamicin or tobramycin, or ceftazidime combined with aminoglycosides should be used (25). Long-term intravenous antibacterial therapy is a necessary means for IE treatment, and a reasonable course of antibiotics can improve the prognosis of patients to some extent (26). However, unfortunately, statistical analysis on the duration of antibacterial drug use in the two groups was not conducted, which warrants further research and analysis. Research has shown that early surgical treatment of IE can effectively reduce the risk of systemic embolism, improve heart function, control infection and significantly reduce overall mortality (27). Furthermore, HD-IE patients have a low surgical rate and poor postoperative prognosis (24). However, in the present study, there was no significant difference between the surgical treatment of IE patients and the survival prognosis of patients, which may be due to the small sample size. Therefore, whether there is a significant difference in the long-term survival rate of these patients with early surgical intervention and simple medical conservative treatment remains to be further studied.

Haemodialysis is an independent risk factor affecting the survival of patients with IE. Antibiotic treatment or surgical treatment should be strongly recommended for active and effective treatment. Larger sample size studies are required to help improve the survival of haemodialysis patients with IE.

Acknowledgements

Availability of data and materials

All data generated and/or analysed during this study are included in this published article.

Authors' contributions

YJH and CSY designed and performed the study together, and they are responsible for data analysis, writing and revising the manuscript. YJH, CSY, KYX, KLW, XMW, MYL, YW, QSY and LLY are responsible for data collection and detection of samples. XY, MW and SJQ were responsible for data analysis, interpretation of the data, obtaining ethics approval and confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed according to the Declaration of Helsinki and approved by the local ethics board of Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine (Hangzhou, China). Individual patient consents were waived on the condition that all patients were deidentified before analysis since this study was a retrospective analysis.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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