Comparison of clinical characteristics and outcomes of infective endocarditis between haemodialysis and non-haemodialysis patients in China

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Abstract

Objective: To clarify differences in clinical characteristics and outcomes between patients with infective endocarditis (IE) receiving long-term haemodialysis (HD group) and those not receiving haemodialysis (non-HD group).

Methods: Medical records of patients with IE, admitted to hospital between January 2010 and December 2017, were retrospectively studied. Clinical characteristics and outcomes were compared between HD and non-HD groups. Risk factors for IE were assessed by COX regression.

Results: Twenty-one HD and 143 non-HD patients were included. Predisposing heart conditions were more frequently observed in the non-HD versus HD group (90.9% versus 19.0%). Inappropriate antibiotic therapy rate before admission and proportion of methicillin-resistant *Staphylococcus aureus* and *Enterococcus*-associated IE was higher in the HD versus non-HD group. In the HD group, fewer patients underwent heart surgery (9.5% versus 51.7%), all-cause in-hospital mortality was higher (52.4% versus 21%), and survival rate was lower versus the non-HD group. COX regression analysis revealed that haemodialysis, use of central venous catheter (CVC) and inappropriate antibiotic therapy before admission increased IE mortality, while surgery improved long-term prognosis.

Conclusions: Haemodialysis patients with IE may have higher mortality and lower survival rates than patients with IE not receiving haemodialysis. Haemodialysis, use of CVC and inappropriate

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antibiotic therapy before admission may increase IE mortality. Surgery may improve long-term prognosis.

Introduction

With the maturity and advancement of renal replacement therapy, patients with infective endocarditis (IE) who are receiving chronic haemodialysis have gradually attracted widespread attention. The relative risk of IE in patients on haemodialysis may be as much as 16.9 times the IE risk in the general population.[1] Moreover, the incidence of IE in haemodialysis patients can be up to 3–10 per 100 000 person-years.[2–4] Patients with IE who are not on haemodialysis have a 90–95% cure rate,[5,6] whereas in haemodialysis patients with IE, the survival rate is approximately 40%, 30%, and 20% at 1, 2, and 3 years, respectively.[7] However, the epidemiological characteristics, clinical features, and related prognoses of haemodialysis patients with IE vary between different regions.[1–4,7,8] Despite a very large population of patients receiving haemodialysis in China, there are few relevant reports on the haemodialysis population with IE. Data from Taiwan showed a mean annual incidence of IE in haemodialysis patients of 201.4 per 100 000 person-years, which was approximately 26.5 times the overall prevalence of IE, and an in-hospital mortality rate of 23.5% from 1998 to 2008.[9] In addition, since patients on haemodialysis require extracorporeal circulation, infections are more likely to spread, and fever in haemodialysis patients with IE is more common.[6,8,9] Volume management is strict and dry weight is kept stable in haemodialysis patients; thus, symptoms of IE differ from the common heart failure symptoms of IE seen in the general population.[2,9,10] Given the many opportunities for contact with doctors, fever in haemodialysis patients is easily misdiagnosed as a community infection, which leads to an increased probability of antibiotic use, making the bacterial spectrum very different from that in the general population.[9,10] Therefore, mastering the characteristics of special patients, such as haemodialysis patients with IE, is more conducive to their proper diagnosis and treatment.

The aim of the present study was to retrospectively describe and outline the clinical characteristics of haemodialysis patients with IE versus those with IE who are not on haemodialysis, as well as to determine the prognostic factors of IE in haemodialysis patients as a whole in mainland China.

Patients and methods

Study population

This single-centre, retrospective study included consecutive patients who were admitted with IE to the Affiliated Hospital of Qingdao University between January 2010 and December 2017. All consecutive patients with a discharge diagnosis of IE according to the modified Duke criteria were enrolled.[11] Patients were excluded if they had: (1) a history of acute kidney injury (AKI); (2) chronic kidney disease (CKD) and were not receiving haemodialysis; (3) an unconventional diagnosis; or

(4) incomplete data. For patients who experienced more than one episode of IE during the study period, only the first episode was considered.

The study was approved by the Ethics Committee of The Affiliated Hospital of Qingdao University (Approval No. QYFYWZLL25643). Informed consent was not required as the study comprised a retrospective analysis of anonymized data that was extracted from patient records.

Data regarding patient demographics, predisposing heart conditions, onset symptoms, time between onset to diagnosis, blood parameters, microbial species, haemodialysis access type, echocardiography results, surgical and antibiotic treatments, and cause of death were extracted from patient records. For analyses, patients were categorised into those on haemodialysis (HD-IE group) and those not receiving haemodialysis (non-HD-IE group). Haemodialysis patients were also subdivided into haemodialysis access type.

Definitions of study variables

A predisposing heart condition was defined as a history of prosthetic cardiac valve replacement, congenital cardiac malformation, rheumatic and other acquired valvular dysfunctions, hypertrophic cardiomyopathy, or mitral valve prolapse with valvular regurgitation.[11]

All patients with CKD who had initiated haemodialysis and required long-term haemodialysis before the diagnosis of IE were captured. Patients with AKI who concomitantly required haemodialysis, and patients with CKD who were not receiving long-term haemodialysis, were excluded.[12]

Appropriate antibiotic therapy was defined as the administration of at least one antimicrobial agent to which the causative pathogen was susceptible within 24 h upon admission, or after the onset of IE, via the appropriate route and with the accurate dosage.[13] Any antibiotic therapy that was inconsistent with the above description was defined as inappropriate antibiotic therapy.

The primary outcome of interest was all-cause in-hospital mortality, defined as 'died' during hospitalization.[12]

Statistical analyses

Continuous variables are presented as mean $\pm$ SD or median (range), with comparisons performed using Student's *t*-test or Mann–Whitney *U*-test. Categorical variables are reported as numbers and percentages, and univariate analysis was performed using Pearson's χ^2-test or Fisher's exact test. Overall survival was estimated using the Kaplan-Meier method. To determine the associations of haemodialysis status with outcomes of interest (in-hospital mortality), COX regression models were constructed. A *P*-value of <0.05 was considered statistically significant. All data were analysed using SPSS software, version 22.0 (SPSS Inc. Chicago, IL, USA).

Results

Patient characteristics

A total of 247 consecutive patients with IE were enrolled. Following screening of records, 83 patients were excluded and a total of 164 patients were included in the study (Figure 1). At the onset of IE, 21 patients (12.8%) were under chronic haemodialysis treatment (HD-IE group) and 143 patients (87.2%) were not receiving haemodialysis (non-HD-IE group).

Median patient ages in the HD-IE and non-HD-IE groups were 48 (26–80) years and 48.5 (22–84) years, respectively (Table 1). There were no differences in the distributions of age and sex between the two groups. Predisposing heart conditions were more frequently observed in the
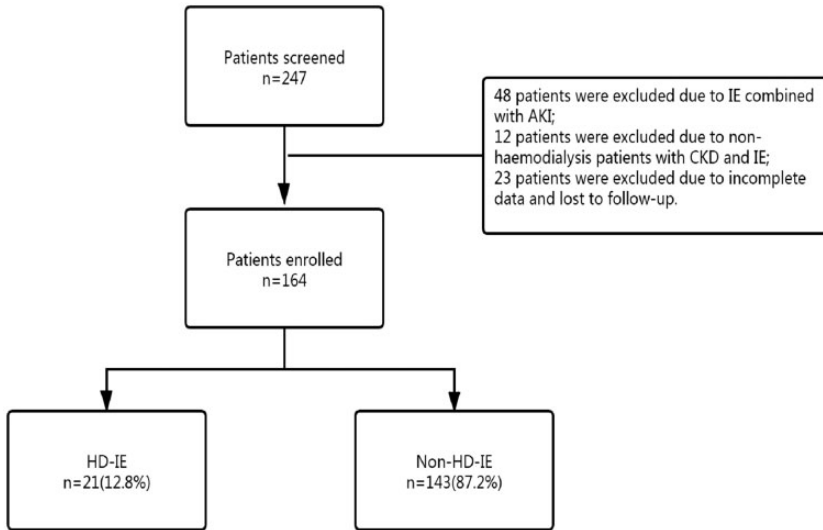
Figure 1. Flowchart showing selection of patients with infective endocarditis (IE) for inclusion into the study. AKI, acute kidney injury; CKD, chronic kidney disease; HD, haemodialysis.

Table 1. Comparison of demographic and clinical characteristics between haemodialysis (HD) and non-haemodialysis (non-HD) patients with infective endocarditis (IE).

	Study group		
Characteristic	HD-IE ($n = 21$)	Non-HD-IE ($n = 143$)	Statistical significance
Age, years	48 (26–80)	48.5 (22–84)	NS
Male	11 (52.4)	73 (51.0)	NS
Predisposing heart conditions	4 (19.0)	130 (90.9)	$P < 0.05$
Access type			
CVC	13 (61.9)	No IV drug use/misuse	
AVF	8 (38.1)		
Presenting clinical syndrome			
Fever	19 (90.5)	86 (60.1)	$P = 0.007$
Heart failure	2 (9.5)	110 (76.9)	$P < 0.01$
Embolism	1 (4.8)	14 (9.8)	NS
Time from onset to diagnosis, days	24 (14–67)	15 (7–33)	$P < 0.05$
Inappropriate antibiotic therapy before admission	21 (100)	39 (27.3)	$P < 0.05$
Laboratory test			
WBC	11.02 ± 6.82	10.66 ± 6.97	NS
HB	79.0 ± 10.79	105.87 ± 26.31	$P < 0.05$
SCr	896.23 ± 248.51	123.60 ± 61.37	$P < 0.05$
ESR	51.77 ± 41.61	55.04 ± 38.83	NS
ALB	26.66 ± 4.17	30.34 ± 5.94	$P < 0.05$

(continued)

Table 1. Continued.

| Characteristic | Study group | | Statistical significance |
	HD-IE (n = 21)	Non-HD-IE (n = 143)	
Causative bacterial species			
Staphylococcus aureus	4 (19)	9 (6.3)	NS
MRSA	3 (14.3)	1 (0.7)	*P* < 0.05
Others			
Coagulase-negative staphylococci	0	24 (17.0)	NS
Enterococcus	4 (19)	5 (3.5)	*P* = 0.02
Gram-negative bacilli	2 (9.5)	8 (5.6)	NS
Streptococcus	0	31 (21.7)	*P* = 0.01
Fungus	1 (4.8)	2 (1.4)	NS
Culture negative	10 (47.6)	64 (44.8)	NS
Valve involvement			
Mitral valve	13 (61.9)	107 (74.8)	NS
Tricuspid valve	2 (9.5)	16 (11.2)	NS
Aortic valve	6 (28.6)	22 (15.4)	NS
Artificial valve	0	4 (2.8)	NS
Surgery	2 (9.5)	74 (51.7)	*P* < 0.01
All cause in-hospital mortality	11 (52.4)	30 (21.0)	*P* < 0.01

Data presented as mean ± SD, median (range) or *n* (%) prevalence.
CVC, central venous catheter; AVF, arteriovenous fistula; WBC, white blood cells; HB, haemoglobin; SCr, serum creatinine; ESR, erythrocyte sedimentation rate; ALB, serum albumin; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.
NS, no statistically significant between-group difference (*P* > 0.05).

non-HD-IE group than in the HD-IE group (90.9% versus 19.0%; *P* < 0.05). Onset symptoms differed between the two groups. The most common onset symptom in the HD-IE group was fever (90.5%; *P* < 0.01 versus non-HD-IE group), whereas heart failure was the most common onset symptom in the non-HD-IE group (76.9%; *P* < 0.01 versus HD-IE group). Time from onset to diagnosis also differed between the two groups (24 days versus 15 days, HD-IE versus non-HD-IE groups, respectively; *P* < 0.05; Table 1).

The white blood cell count and erythrocyte sedimentation rate were not significantly different between the two groups (*P* > 0.05; Table 1). The haemoglobin and serum albumin levels were significantly lower in the HD-IE patients (79.0 versus 105.87 and 26.66 versus 30.34, respectively) and serum creatinine levels (SCr) were significantly higher (896.23 versus 123.60) compared with levels in the non-HD-IE group (all *P* < 0.05; Table 1).

Microbiological features

The pathogen isolated from blood cultures differed between the HD-IE and non-HD-IE groups (Table 1). *Staphylococcus aureus* and *Enterococcus* were the most common pathogens in HD-IE group, while *Streptococcus* were the most pathogens found in the non-HD-IE group (19% versus 6.3%, *P* > 0.05; 19% versus 3.5%; and 0 versus 21.7%, respectively;

$P < 0.05$). In addition, the proportion of MRSA-associated IE was significantly higher in the HD-IE group compared with the non-HD-IE group (14.3% versus 0.7%; $P < 0.05$). The incidence of culture-negative IE was similar in both groups (47.6% versus 44.8%, HD-IE and non-HD-IE respectively; $P > 0.05$).

Haemodialysis patients were subdivided according to haemodialysis access, into a central venous catheter (CVC) group (61.9%) and arteriovenous fistula (AVF) group (38.1%). Comparison of microbiological profiles revealed no statistically significant differences between the two subgroups ($P > 0.05$; Figure 2a).

Echocardiographic findings

Vegetations identified through transthoracic echocardiography and transoesophageal echocardiography were mostly found on the mitral valve in the HD (61.9%) and non-HD (74.8%) groups (Table 1). No statistically significant difference was observed between the two groups in terms of vegetation locations ($P > 0.05$).

Surgery and inappropriate antibiotic therapy before admission

The number of patients who underwent surgery for active IE during hospitalization was significantly lower in the HD-IE group than in the non-HD-IE group
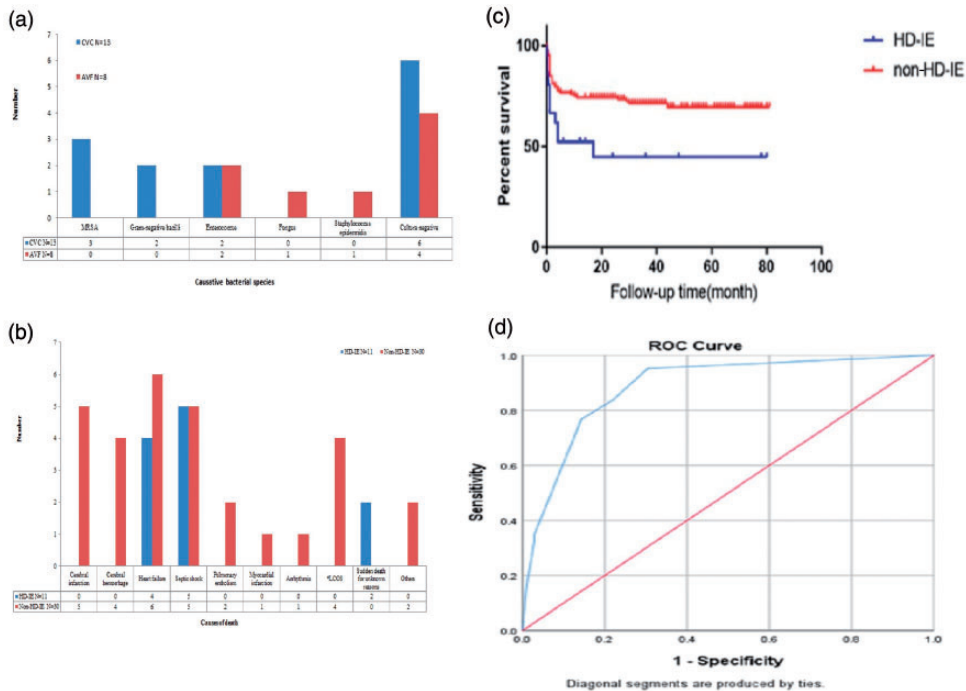

Figure 2. Results charts for haemodialysis patients with infective endocarditis (HD-IE group) and non-haemodialysis patients with IE (non-HD-IE group): (a) Microorganisms identified in HD-IE group, according to type of vascular access ($P > 0.05$); (b) Analysis of death causes between the HD-IE and non-HD-IE groups ($P > 0.05$); (c) Survival curves in the HD-IE and non-HD-IE groups ($P < 0.05$, hazard ratio 0.296, 95% confidence interval [CI] 0.1184, 0.7403); and (d) Receiver operating characteristic (ROC) curve with an area under the curve value of 0.886 (95% CI 0.828, 0.944; $P < 0.001$). HD, haemodialysis; CVC, central venous catheter; AVF, arteriovenous fistula; LCOS, low cardiac output syndrome.

(9.5% versus 51.7%; $P < 0.05$; Table 1). Moreover, the rate of inappropriate antibiotic therapy before admission was significantly higher in the HD-IE group than in the non-HD-IE group (100% versus 27.3%; $P < 0.05$).

Mortality and causes of death

All-cause in-hospital mortality was significantly higher in the HD-IE group versus the non-HD-IE group (52.4% versus 21.0%; $P < 0.01$; Table 1). Causes of death were further analysed, and the top three factors were found to be septic shock, cerebral embolism, and heart failure (Figure 2b). There were no statistically significant differences in cause of death between the two groups ($P > 0.05$, Figure 2b).

Survival curves and risk factors associated with long-term outcomes

Analysis of survival curves between the two groups showed a significantly lower survival rate in the HD-IE group compared

with the non-HD-IE group (hazard ratio 0.296, 95% CI 0.1184, 0.7403; $P < 0.05$; Figure 2c). COX regression analysis was employed to identify risk factors for overall mortality, including haemodialysis on survival duration. According to the COX regression analysis, haemodialysis, use of CVC and inappropriate antibiotic therapy before admission were related to increased IE mortality, while surgery was shown to improve long-term prognosis (Table 2). Receiver operating characteristic curve analyses using this model (combined factors of haemodialysis, use of CVC and inappropriate antibiotic therapy as predictive of mortality) revealed an area under the curve of 0.886 (95% CI 0.828, 0.944; $P < 0.001$; Figure 2d).

Discussion

The current retrospective study assessed the differences between haemodialysis and non-haemodialysis patients with IE in a single centre in mainland China. To the best of

Table 2. Risk factors for all-cause mortality in haemodialysis and non-haemodialysis patients with infective endocarditis.

Risk factor	Univariable analysis		Multivariable analysis	
	HR (95% CI)	Statistical significance	HR (95% CI)	Statistical significance
HD	121.313 (9.128, 1612.317)	$P < 0.001$	72.436 (6.003, 874.070)	$P = 0.001$
CVC	6.490 (1.607, 26.206)	$P = 0.009$	7.285 (1.894, 28.017)	$P = 0.004$
Inappropriate antibiotic therapy before admission	13.925 (5.762, 33.650)	$P < 0.001$	13.116 (5.557, 30.956)	$P < 0.001$
HB	0.989 (0.970, 1.007)	NS		
ALB	1.008 (0.935, 1.086)	NS		
Age	0.991 (0.967, 1.015)	NS		
Predisposing heart conditions	0.674 (0.253, 1.791)	NS		
Surgery	0.211 (0.092, 0.483)	$P < 0.001$	0.218 (0.104, 0.454)	$P < 0.001$

HD, haemodialysis; CVC, central venous catheter; HB, haemoglobin; ALB, serum albumin; HR, hazard ratio; CI, confidence interval.
NS, no statistically significant between-group difference ($P > 0.05$).

the present authors' knowledge, this study is one of the few that compares clinical features and outcomes among patients with IE and similar backgrounds between those on haemodialysis and those not receiving haemodialysis in China. Susceptibility to IE in haemodialysis patients is multifactorial, with several factors playing an essential role in the predisposition and development of IE. Some of these factors are related to a higher prevalence of degenerative valve disease and calcification, and others to bacteraemia during repeated vascular access puncture and uraemia-related immune-system deficiencies.[14]

In the present study, haemodialysis patients had a lower rate of predisposing heart conditions than non-haemodialysis patients. IE is a heterogeneous disease with a highly variable clinical presentation, and congenital heart disease remains the leading predisposing heart disease for IE.[8] The results of the present study showed that the presenting clinical symptom in haemodialysis patients was mostly fever, whereas heart failure was the most prevalent presenting symptom in non-haemodialysis patients. Chronic haemodialysis makes IE complicated and concealed. In the present authors' experience, during the process of haemodialysis, infection easily spreads, and chills are common during dialysis; haemodialysis has strict volume management, and the symptoms of heart failure are relieved after haemodialysis ultrafiltration, making fever a prominent symptom.[10] These factors may be more facilitative toward diagnosis in patients with haemodialysis than in the general population, however, in the present study, the time from onset to diagnosis was significantly longer for haemodialysis patients than for non-haemodialysis patients. Uremic patients are known to be prone to develop multiple infections,[8,15] particularly in the respiratory system; thus, the existence of IE is easily ignored. Moreover, the diagnostic criteria for IE requires the discovery of vegetation,[9] which cannot be determined by fever alone. Sufficient time is also needed to carry out repeated cardiac ultrasound monitoring and blood culture, which are undoubtedly helpful for the diagnosis of IE. Whether Duke's criteria for IE diagnosis adequately apply to haemodialysis patients with IE remains unclear considering the lower sensitivity of echocardiography and the unfeasibility of urinalysis in this setting.[16]

Haemodialysis patients with IE were shown to have a higher frequency of inappropriate antibiotic therapy before admission in the present study, and to the authors' knowledge, this observation is not well described in previously published studies. This may indicate a remarkably high rate of antibiotic use in haemodialysis patients in China. Most importantly, this situation may mask the natural course of IE resulting in sustained bacteraemia, leading to the emergence of a large number of drug-resistant bacteria and diagnostic uncertainty. In addition, the present COX analysis showed that inappropriate antibiotic therapy may affect prognosis of IE patients. IE caused by skin commensal bacteria and nasal *S. aureus* in haemodialysis patients has been confirmed,[17–19] however, the present study did not reveal significant differences in microbiological profiles between the CVC and AVF groups. A previous study reported that the causative pathogen is *S. aureus* in 40–63.6% of haemodialysis patients with IE, and haemodialysis patients have a higher proportion of MRSA than non-haemodialysis patients.[20] The present study identified the microbiological aetiology of IE as MRSA and *Enterococcus* in the majority of haemodialysis patients. By contrast, *Streptococcus* was the main pathogen in non-haemodialysis patients during the same period. It is reasonable to assume that *Enterococcus* infection is more serious, and

in some areas, even exceeds the harmfulness of *Staphylococci*. Additionally, there was a very high culture-negative rate in both of the present study groups, which shows that rapid and accurate diagnosis in the case of suspected IE is a major challenge in this disease.

The rate of surgery in haemodialysis patients ranges from 8–50%.[16] In line with other published findings,[16] the rate of cardiac surgery was significantly lower in the present haemodialysis group than in the non-haemodialysis group. Cardiac surgery carries greater risk for haemodialysis patients, due to multiple complications, and there is still a lack of data regarding postoperative mortality and causes in haemodialysis patients with IE. However, the present COX analysis revealed that surgery may improve long-term prognosis. Postoperative survival in haemodialysis patients with IE is well known to be dependent on operative time, rapid successful surgery, and proper postoperative management.[21] Although mortality in haemodialysis patients with IE is high irrespective of whether they undergo surgery, the present authors consider it essential to identify those patients who may benefit most from surgical treatment.[16,21] At present, most viewpoints suggest that once surgical treatment is decided, the operation should be performed as soon as possible before other complications, such as stroke, occur.[22]

Notably, all-cause in-hospital mortality was shown to be much higher in haemodialysis patients with IE patients than in non-haemodialysis patients with IE, and haemodialysis patients with IE had a lower survival rate than non-haemodialysis patients with IE, which was consistent with previous research.[16] The leading causes of death were found to be septic shock, cerebral embolism, and heart failure for IE patients in the present centre, and no difference was found between haemodialysis and non-haemodialysis groups.

Subsequent COX regression analysis and found that haemodialysis, use of CVC and inappropriate antibiotic therapy were associated with increased IE mortality, which is consistent with previous research.[8,23] Prior studies also have reported that advanced age, diabetes, Staphylococcal infection, arrhythmia, cardiac index during hospitalization, and central nervous system embolization were independent predictors of high mortality in haemodialysis patients undergoing valvular replacement.[7,24,25]

Some limitations of the present single-centre study should be noted. The study sample was restricted to patients with echocardiography-confirmed IE and excluded those with possible IE but without vegetations on heart valves, leading to a selection bias in disease severity. In addition, the sample size of haemodialysis patients was small; therefore, it prevented the detection of other prognostic factors associated with mortality. Nevertheless, it is crucial to learn about the clinical differences between haemodialysis and non-haemodialysis patients with IE. To understand the impact of haemodialysis on IE, it remains necessary to investigate differences in the incidence of IE between patients with end-stage renal disease who are either receiving or not receiving haemodialysis, and to compare groups of patients with different pathways, to further clarify the impact of different dialysis pathways on IE.

In conclusion, haemodialysis patients with IE may have higher mortality and lower survival rates, and diagnosis of IE may be more difficult to confirm, than in non-haemodialysis patients with IE. Drug-resistant bacteria and specific pathogen infections should be monitored. Haemodialysis, use of CVC and inappropriate antibiotic therapy before admission may increase IE mortality. Finally, it is essential to identify those haemodialysis patients with IE who could benefit most from

surgical treatment, as surgery may improve long-term prognosis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

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