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Original Article

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Mortality risk factors in chronic haemodialysis patients with infective endocarditis

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Abstract

Background. It is well documented that infective endocarditis (IE) is strongly associated with morbidity and mortality in haemodialysis (HD) patients. Less clear are the mortality risk factors for IE, particularly in an urban African-American dialysis population.

Methods. IE patients were identified from the medical records for the period from January 1999 to February 2004 and confirmed by Duke criteria. The patients were classified as 'survivors' and 'non-survivors' depending on in-hospital mortality, and risk factors for IE mortality were determined by comparing the two cohorts. Survivors were followed as out-patients with death as the endpoint.

Results. A total of 52 patients with 54 episodes of IE were identified. A catheter was the HD access in 40 patients (74%). Mitral valve (50%) was the commonest valve involved, and Gram-positive infections accounted for 87% of IE. In-hospital mortality was high (37%) and valve replacement was required for 13 IE episodes (24%). On logistic regression analyses, mitral valve disease [$P = 0.002$; odds ratio (OR) = 15.04; 95% confidence interval (CI) = 2.70–83.61] and septic embolism ($P = 0.0099$; OR = 9.56; 95% CI = 1.72–53.21) were significantly associated with in-hospital mortality. Using the Cox proportional hazards model, mitral valve involvement ($P = 0.0008$; hazard ratio 4.05; 95% CI = 1.78–9.21) and IE related to drug-resistant organisms such as methicillin-resistant *Staphyloccus aureus* and vancomycin-resistant *Enterococcus* sp. ($P = 0.016$; hazard ratio 2.43; 95% CI = 1.18–5.00) were associated with poor outcome after hospital discharge.

Conclusions. IE was associated with high mortality in our predominantly African-American dialysis population, when the mitral valve was involved, or septic emboli occurred and if MRSA or VRE were the causal organisms.

Keywords: catheters; endocarditis; end-stage renal disease; mortality; septic emboli

Introduction

While Sir William Osler is credited for his initial clinical description of infective endocarditis (IE), Blagg and his associates [1] were the first to report this complication in haemodialysis (HD) patients. Infection is a significant contributor to mortality in dialysis patients, next only to cardiovascular disease [2], and specifically, IE can be a catastrophic complication. Among the high-risk groups for IE (i.e. intravenous drug users, native/prosthetic valve disease etc.), HD patients deserve special mention. The incidence of IE is at least 10–18 times higher in dialysis patients than in the general population [3] and is associated with higher in-hospital and 1-year mortality [4–6]. In addition, IE leads to lengthy and expensive hospitalizations [4,5,7]. HD catheters contribute significantly to the increasing incidence of bacteraemia [8] and as a result, to IE. Even though the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines clearly recommend native arteriovenous fistula (AVF) as the preferred vascular access [9], a substantial proportion (28%) of chronic dialysis patients continue to use a catheter as a permanent HD access [10].

Prior studies have described the epidemiology of IE and risk factors for mortality [3–7,11] in a predominantly non-African-American dialysis population and had focused on mortality during hospitalization related to IE. In this retrospective study, we sought to identify risk factors for mortality in our large, urban dialysis population that is composed predominantly of patients of African-American ethnicity.

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In addition, we extended our observation to overall survival of these subjects with post-hospitalization follow-up.

Materials and methods

Patients

All end-stage renal disease (ESRD) patients discharged from the Henry Ford Hospital, Detroit, with a diagnosis of IE, between January 1999 and February 2004, were identified from the electronic databases using International Classification of Disease-9 (ICD-9) codes for ESRD (585.0) and IE (421.0, 421.1 and 421.9). The average number of patients undergoing chronic HD is approximately 1000 per year, about 90% of these patients are of African-American ethnicity. This study was approved by the local institutional review board.

Data collection

Demographic, clinical, echocardiographical and microbiological information was obtained from the patient's chart or the institution's computerized medical records (Careplus®). Collected data included age, gender, ethnic origin, history of diabetes mellitus (DM), hypertension, intravenous drug abuse (IVDA), hepatitis B and hepatitis C serologies, serum albumin, type of HD access, and the time interval from the placement of access to the diagnosis of IE. Microbiological data comprised the type of organism isolated from blood and the catheter tip. Transthoracic (TTE) and transesophageal (TEE) echocardiogram reports, type of valve involved and cardiac complications of IE were reviewed for the diagnosis.

To identify the risk factors associated with mortality during hospitalization, the identified subjects were divided into two groups depending on survival during the hospitalization (non-survivors in group A and survivors in group B) and patient characteristics were compared. The cohort of patients who survived the hospitalization was followed for a period of 1–59 months with death as the endpoint. Follow-up data was obtained from the computerized records of out-patient, in-patient visits and dialysis rounds.

Definitions

Modified Duke criteria were used to define IE and only the *definite* IE cases were included i.e. if the patient had two major criteria or one major and three minor criteria or five minor criteria [12]. Access that was utilized for HD just prior to hospitalization was defined as the vascular access for dialysis. Duration of access was defined as the time interval between the placement of that access and the time of hospitalization. All surgeries done on cardiac valves during that index hospitalization were defined as valve surgery. Septic embolization was determined according to the clinical evaluation documented in the charts and confirmed by radiological tests in some cases.

Statistical analyses

The demographic and clinical data are presented as the proportion of patients in each group or as the mean ± standard deviation. Fisher's exact test or two-tailed Student's *t*-test were used for statistical analysis as appropriate. A *P*-value of <0.05 was considered statistically significant.

The patient characteristics that individually showed statistically significant association with mortality during hospitalization were the only variables included in the final multivariate analyses. Stepwise logistic regression analysis, using the SAS logistic procedure, was applied. Outcomes of the analysis included *P*-values, odds ratios (ORs) and hazard ratios and their 95% confidence limits. To assess the impact of IE on overall survival, Cox proportional hazard regression analysis was performed on the entire cohort of patients. Survival curves were calculated by Kaplan–Meier method and the curves were compared by the log-rank test.

Results

Using the Duke criteria, 54 episodes of definite IE were identified in 52 ESRD subjects during the 5-year study period. The average number of patients who underwent maintenance HD at our institution during the study period was ~1000 patients/year, translating to an incidence of 11 cases per 1000 patient-years. The patient's clinical and demographic data are shown in Table 1. While gender distribution was equal, African-Americans accounted for the majority of cases of IE (85%). Even though the mean age was 60 years (range 36–82), a significant proportion (27%) of patients were $\geq$70 years of age. History of DM and IVDA was present in 42 and 12% of patients, respectively. A history of prior IE was noted in only 12% patients.

In our series, 40 patients (74%) had a catheter as the HD vascular access at the time of diagnosis of IE, while the other patients had prosthetic arteriovenous grafts (13%), subcutaneously implanted dialysis access ports (Life-Site®) (9%) or native arteriovenous fistulae (4%). Among the catheter patients, the majority (72%) had cuffed, tunnelled catheters. The mean duration (±SD) of the cuffed, tunnelled catheter was 24 ± 26 weeks.

While a TTE study was able to identify vegetations in 13% of patients, the majority of patients (87%) had TEE to confirm the diagnosis. In our series, mitral valve (50%) was the commonest valve involved (Table 2), followed by aortic (43%) and tricuspid valve (19%). *Staphylococcus aureus* (40%) and *Enterococcus* (33%) were the most common microbiological pathogens.

Nineteen patients (37%) died during the hospitalization for IE and 13 more patients died during the follow-up period. Among the survivors, the mean (±SD) duration of hospital stay was 18 ± 11 days. Septic emboli related to IE were noted in 15 patients (28%) and two-thirds of those patients ($n = 10$) died

Table 1. Characteristics of ESRD patients admitted with IE

	n (%)
Number of patients (*n*)	52
Number of IE episodes	54
Age (years)[a]	60 ± 12
Age	
30–39	1 (2%)
40–49	13 (25%)
50–59	13 (25%)
60–69	11 (21%)
≥70 years	14 (27%)
Gender (female/male)	48%/52%
Ethnicity	
African-American	44 (85%)
Caucasian	8 (15%)
History of diabetes mellitus	22 (42%)
History of hypertension	41 (79%)
History of intravenous drug use	6 (12%)
Prior history of IE	6 (12%)
Hepatitis C antibody (+)	12 (23%)
Hepatitis B surface antigen (+)	2 (4%)
Serum albumin (gm/dl)[a]	2.9 ± 0.6
Dialysis access[b]	
Uncuffed catheter	1 (2%)
Cuffed tunnelled catheter	39 (72%)
Arteriovenous grafts (AVG)	7 (13%)
Arteriovenous fistula (AVF)	2 (4%)
Life-Site®[c]	5 (9%)
Duration of cuffed catheter (weeks)[a]	24 ± 26
Valve[b]	
Native valve	47 (87%)
Prosthetic valve	7 (13%)

[a]Entries are represented as mean ± SD.
[b]Percentage in parenthesis was calculated as proportion of IE episodes.
[c]Implantable subcutaneous haemodialysis port.

Table 2. Valve involvement and the type of organism associated with infective endocarditis in haemodialysis patients

	n (%)
Echocardiogram	
Valve involvement	
Mitral valve	27 (50)
Aortic valve	23 (43)
Tricuspid valve	10 (19)
Multiple valve	5 (9)
Microbiology	
MSSA[a]	11 (20)
MRSA[b]	11 (20)
Enterococcus	18 (33)
VRE[c]	4 (7)
S. epidermis	12 (22)
Resistant org [*MRSA* + *VRE*]	15 (28)
Gram negative organisms	7 (13)
Negative blood culture	1 (2)
Polymicrobial	10 (19)

[a]MSSA: methicillin-sensitive *S. aureus*.
[b]MRSA: methicillin-resistant *S. aureus*.
[c]VRE: vancomycin-resistant *Enterococcus* sp.

during hospitalization. The sites of septic embolism, in descending order of frequency, were as follows: brain ($n=7$), joints ($n=4$), extremities ($n=3$), spleen ($n=2$), kidneys, liver and lung ($n=1$).

Table 3. Comparison between survivors and non-survivors of IE-related hospitalization

	Group A Non-survivors ($n=19$)	Group B Survivors ($n=33$)	*P*-value
Male gender	11 (58%)	17 (51%)	NS
Age (years)[a]	61 ± 12	59 ± 12	NS
Age ≥65 years	7 (37%)	12 (36%)	NS
African-Americans	17 (89%)	31 (94%)	NS
History of DM	6 (32%)	17 (51%)	NS
IV Drug use	1 (5%)	5 (15%)	NS
Serum albumin[a]	2.6 ± 0.43	3 ± 0.6	**<0.007**
Access: Catheters	14 (74%)	26 (79%)	NS
Life site®	2 (11%)	3 (9%)	NS
AVG	1 (5%)	6 (18%)	NS
AVF	2 (11%)	0 (0%)	NS
Duration of cuffed catheter (weeks)[a]	19 ± 13	26 ± 30	NS
Echocardiogram			
Mitral valve	16 (84%)	11 (31%)	**0.0004**
Aortic valve	6 (32%)	17 (49%)	NS
Tricuspid valve	1 (5%)	9 (23%)	NS
Multi-valvular inv	3 (16%)	2 (6%)	NS
LV ejection fraction	58 ± 5%	50 ± 15%	**<0.007**
Microbiology			
MRSA	6 (32%)	5 (14%)	NS
MSSA	5 (26%)	6 (17%)	NS
Polymicrobial	5 (26%)	5 (14%)	NS
Drug-resistant org [MRSA + VRE]	8 (42%)	7 (20%)	NS
Outcome			
Septic embolism	10 (53%)	5 (14%)	**0.004**
Septic emboli to Brain	6 (32%)	1 (3%)	**<0.006**
Valve replacement	5 (26%)	8 (23%)	NS

[a]Mean ± SD.

Death during hospitalization

The clinical and laboratory characteristics were compared between the patients who died during the hospitalization for IE (group A) and the patients who survived that admission (group B). As explained in Table 3, the clinical characteristics such as gender, age ≥65 years, ethnicity, history of diabetes, hypertension or IVDA and the type of dialysis access did not differ significantly between the groups. Similarly, the time interval between the placement of the tunnelled catheter and the diagnosis of IE was not statistically different between the groups (group A: 19 ± 13 weeks *vs* group B: 26 ± 30 weeks, $P=0.31$). Serum albumin was lower in group A (2.6 ± 0.43 g/dl) compared with group B (3 ± 0.6 g/dl) and the difference was statistically significant ($P<0.007$) on univariate analysis. While aortic valve involvement was not associated with an increased risk of death, mitral valve disease was significantly associated with mortality (84 *vs* 31%, $P=0.0004$). Interestingly, survivors of the hospitalization had a lower left ventricular ejection fraction (LVEF) compared with non-survivors (50 ± 15% *vs* 58 ± 5%, $P=0.007$). Overall, the type of microorganism was not statistically different between the two groups. Specifically, IE related to drug-resistant organisms like methicillin-resistant *S. aureus* (MRSA)

and vancomycin-resistant *Enterococcus* sp. (VRE) did not result in excess to in-hospital mortality (42 *vs* 20%, $P = 0.11$). Septic embolus to the brain was significantly associated with an increased risk of death (32 *vs* 3%, $P < 0.006$).

The three patient characteristics (serum albumin, mitral valve disease and septic embolism) in Table 3 that individually showed statistically significant association with survival or non-survival during hospitalization were tested for their joint association using stepwise logistic regression. Only two of the characteristics, mitral valve disease [$P = 0.002$; OR = 15.04; 95% confidence interval (CI) = 2.70–83.61] and septic embolism ($P = 0.0099$; OR = 9.56; 95% CI = 1.72–53.21), were significantly associated with non-survival during that hospitalization.

Follow-up after hospital discharge

Group B patients (survivors, $n = 33$) were followed after hospital discharge and 13 more patients died during follow-up. Using the Cox proportional-hazards model, risk factors for overall mortality were analysed. Mitral valve involvement ($P = 0.0008$; hazard ratio 4.05; 95% CI 1.78–9.21) and IE related to MRSA and VRE ($P = 0.016$; hazard ratio 2.43; 95% CI 1.18–5.00) were significantly associated with poor outcome (Table 4). The negative influence of these two variables on patient survival after hospitalization is illustrated in Figures 1 and 2.

Valve surgery

Valve damage, resulting from IE, necessitated valve replacement surgery in 12 patients for 13 IE episodes (24%). In spite of surgical intervention, five patients died during hospitalization. Left ventricular ejection fraction was identical between the patients who underwent surgery and the patients on medical management (LVEF: 55 ± 13 *vs* $53 \pm 3\%$, $P = 0.58$). As illustrated in Figure 3, the subgroup of patients who underwent surgical repair had similar survival compared with patients who received medical management ($P = 0.97$).

Table 4. Multivariate Cox proportional-hazards model for risk factors associated with post-hospitalization mortality in IE

	Estimate	SE	Chi Square	*P*-value	Hazard ratio (95% CI)
Mitral valve involvement	1.40	0.419	11.15	0.0008	4.05 (1.78–9.21)
IE related to MRSA[a] and VRE[b]	0.89	0.368	5.83	0.016	2.43 (1.18–5.00)

[a]MRSA: Methicillin-resistant *S. aureus*.
[b]VRE: Vancomycin-resistant *Enterococcus* sp.

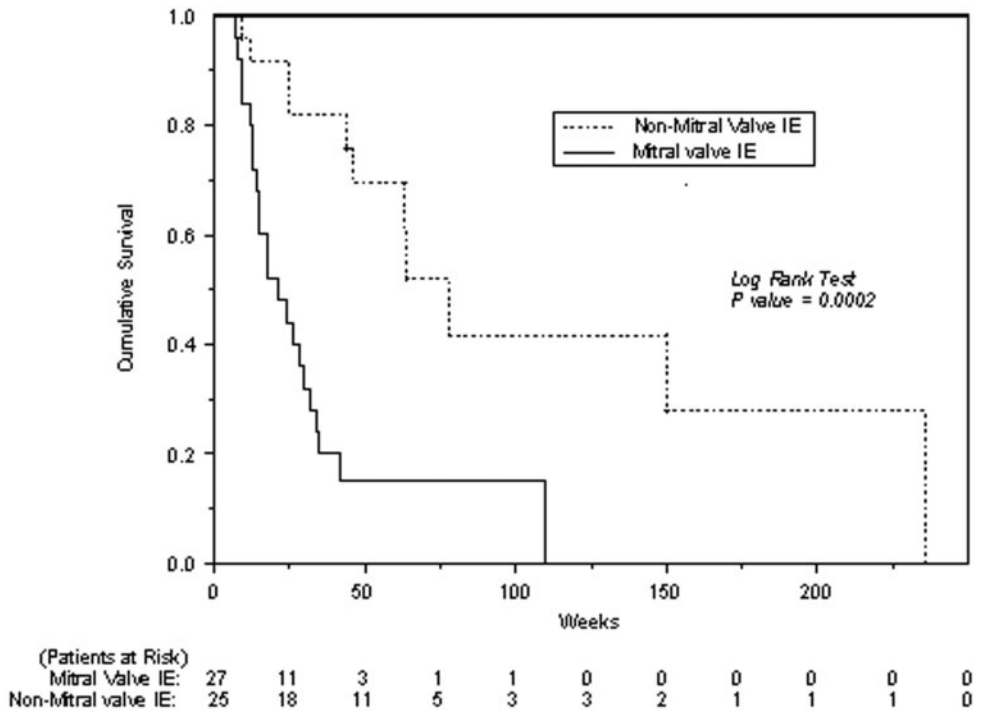

Fig. 1. Patients with mitral valve IE had inferior patient survival when compared with the patients with other valve involvement.

Discussion

In this study, we report 54 episodes of IE in HD patients, making this the largest reported series in this population to the best of our knowledge. The unique attributes of our study compared with the previous publications are that the large majority of the study population is from African-American ethnicity and that we have identified important in-hospital mortality risk factors in these patients. These observations have not been reported in any of the previously published studies. Our data also confirmed the high mortality rate associated with IE, as noted in other studies.

Consistent with prior observations [4,6,7,13], left-sided valvular vegetations were more common in our study population. In addition to being the most commonly involved valve, mitral valve involvement was strongly associated with in-hospital mortality and impacted overall patient survival negatively. In our study, a significantly higher proportion of non-survivors had mitral valve involvement compared with survivors and many of these patients had evidence of septic emboli, including the brain. We speculate that the lower gradient across the mitral valve (as compared with the aortic valve) might have allowed the lesions to attain a larger size before shearing off, leading to clinically significant septic emboli. Interestingly, the non-survivor group had better left ventricular function as compared with survivors at the time of echocardiographic evaluation. This may be related to the fact that non-survivors had a significantly higher rate of mitral valve involvement and IE-related mitral regurgitation and this could have contributed to the erroneous observation of high LVEF.

Septic embolism, specifically embolus to the brain and resulting stroke, was also significantly associated with death, but that effect was confined to in-hospital mortality. However, if the patient survived that hospitalization, embolic episode did not negatively influence survival after hospital discharge.

S. aureus was the most common pathogen in our series and previous studies have reported similar findings [4–7,13,14]. Contrary to earlier observations [11], the type of organism, specifically IE related to MRSA and VRE, did not influence in-hospital mortality. However, we noted that these organisms had an impact on overall patient survival and this was consistent with the observation of Cabell *et al.* [15] in their cohort of IE patients that included dialysis and non-dialysis population.

It is known from earlier studies that hypoalbuminaemia predicts mortality risk in acute illnesses, including bacteraemia, and has been a component of various critical care unit outcome measures [16]. Serum albumin levels may fall acutely with inflammation ('negative acute phase reactant'), acute or chronic stress and increase following resolution or recovery. However in our study, even though hypoalbuminaemia was associated with higher mortality on univariate analysis, it was not independently associated with death on regression analyses. While hypoalbuminaemia has been associated with an increased risk of bacteraemia [17] and IE [3], Chang *et al.* [11] had reported findings similar to our series of lack of association between hypoalbuminaemia and mortality

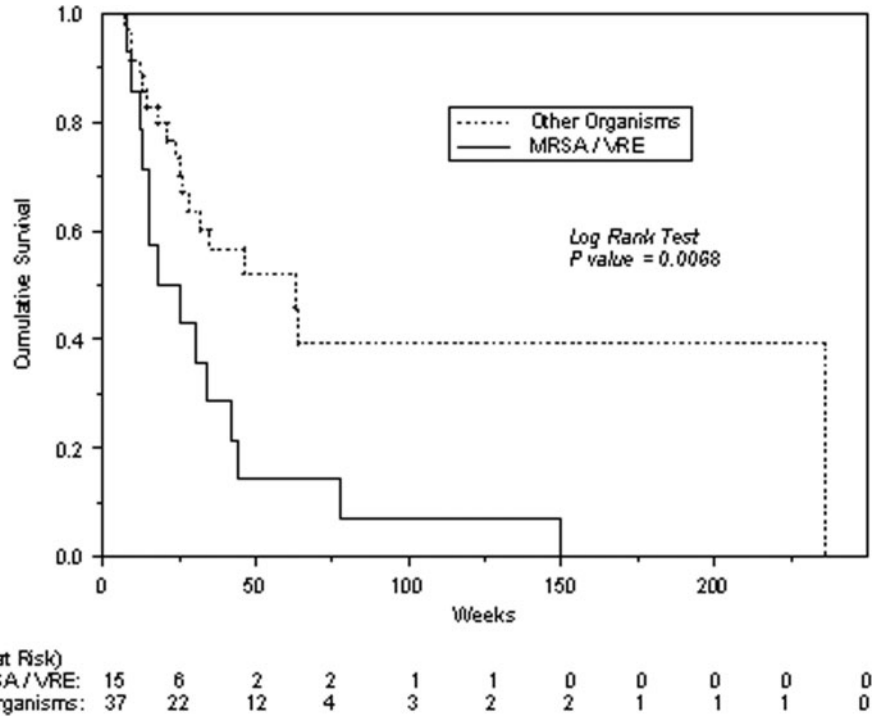

Fig. 2. IE related to drug-resistant organisms such as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) resulted in poor patient survival.

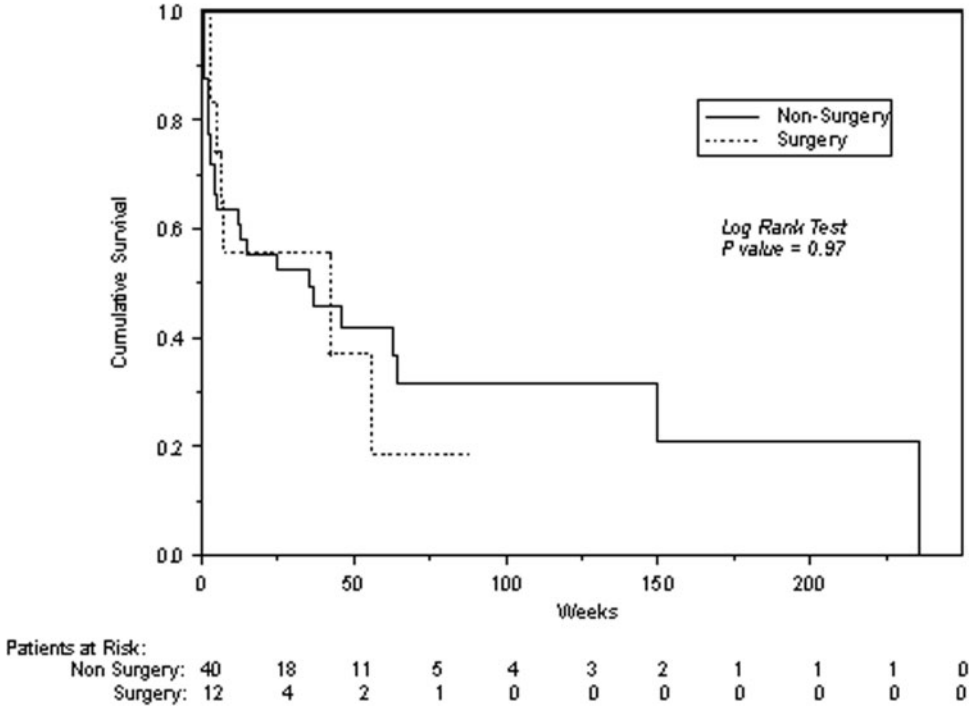

Fig. 3. Comparison of Kaplan–Meier survival curves for a HD patients who underwent valve replacement (surgery group) *vs* medical management (non-surgery group) for infective endocarditis.

in IE patients. A prospective study with larger sample size is required to verify the negative influence of hypoalbuminaemia on survival in HD patients with IE.

Valve replacement surgery did not impact survival in our patients. The American College of Cardiology/American Heart Association task force has defined indications for valvular surgery in patients with native and prosthetic endocarditis [18]. However, the indications in patients with significant comorbid conditions are less clear. Recently, Spies *et al.* [7] reported high perioperative mortality in dialysis patients who underwent valve replacement surgery for endocarditis. It is possible that this intervention may have been employed at an advanced stage of the disease, when serious embolic complications had already set in, and patients selected for surgery may have had severe disease.

The data presented in this study clearly underline the importance of vascular catheters as the source of bacteraemia and IE. Even the recent trend to use cuffed, tunnelled HD catheters instead of the uncuffed catheters has not translated to a significant reduction in the catheter-related bacteraemia in HD patients [19].

Our study has some of the inherent limitations of any retrospective chart review. First, echocardiographic data were only available in selected individuals who may have been clinically ill, with the potential for missing clinically silent disease in other patients. Second, we could have missed data that were not appropriately coded for IE and dialysis patients who were admitted to other hospitals. Third, patients were chosen for surgery or medical management based on individual physician's decision rather than pre-defined study criteria. Hence the lack of efficacy of surgery may just be an observation. The sample size was small and type II (β) error may be high. The small sample size could have also accounted for both the wide 95% CIs and non-statistical significance between the groups with regards to certain variables and outcomes. Fourth, we could not include a control group of HD patients with bacteraemia but without endocarditis, since many such individuals did not undergo echocardiography. Finally, IE related to MRSA and VRE were associated with poor prognosis during follow-up. These organisms may be surrogate markers of multiple hospitalizations and antibiotic therapies. Complete data could not be obtained regarding individual patient's antibiotic use prior to hospitalization. A larger sample needs to be studied prospectively to individually characterize the risk factors and confirm the efficacy of therapeutic options. Our study population was comprised predominantly of urban patients of African-American ethnicity on HD. Hence the mortality risk factors identified in our study may not be applicable to all dialysis patients, including peritoneal dialysis.

In summary, our study has identified mitral valve involvement and clinically evident septic embolism as definite risk factors for in-hospital mortality in HD patients with IE, in addition to confirming the high incidence and high in-patient mortality associated with this disease. Similarly, mitral valve disease and IE related to drug-resistant organisms are associated with poor overall patient survival even after hospital discharge.

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Conflict of interest statement. None declared.

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