**Original
Article**

Long-Term Outcome of Active Infective Endocarditis with Renal Insufficiency in Cardiac Surgery

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Background: The relation between infective endocarditis (IE) and renal insufficiency is uncertain. The aim of this study was to investigate active IE with renal insufficiency in cardiac surgery.

Patients and Methods: A retrospective record review was conducted of all cases with IE from January 1998 to July 2009. We identified 38 patients who had undergone surgical intervention (25 males and 13 females, mean age 57.3 ± 15.2 years, range 23–83 years) of IE as defined by the modified Duke criteria. Indications for surgical intervention included new, severe valvular regurgitation with heart failure, intracardiac abscesses, and recurrent embolic events. All patients were divided two groups; one group comprised patients without renal insufficiency (group N, $n = 28$), the other, those with renal insufficiency (group R, $n = 10$).

Results: Mean age of patients in group R was larger than that in of group N (66.3 ± 10.6 vs. 54.1 ± 15.4 years, $p = 0.0268$), and mean hemoglobin in group R than in group N (8.4 ± 0.9 vs. 10.3 ± 2.5 g/dl, $p = 0.0215$). In the early outcome, hospital death was greater in group R than in group N (20.0% vs. 0.0%, $p = 0.0143$). The 8-year survival was significantly worse in group R than in group N (50.0% vs. 96.4%, log rank test: $p = 0.0042$). Moreover, the 8-year actuarial freedom from cardiac events was significantly worse in group R than in group N (0.0% vs. 60.3%, log rank test: $p = 0.0003$), too. Renal insufficiency predicted an increase in long-term mortality (OR 12.104, 95% CI 1.349–108.641, $p = 0.0259$) and morbidity (OR 10.540, 95% CI 2.173–51.129, $p = 0.0035$).

Conclusions: In IE, renal insufficiency may allow for risk stratification of patients undergoing surgical intervention.

Keywords: infective endocarditis, valvular disease, microorganism, renal insufficiency

Introduction

Acute infective endocarditis (IE) is a clinical challenge that is often associated with high patient morbidity and mortality.¹⁾ Although IE is generally treated using antibiotics, surgical intervention is required in 20% of cases.²⁾ Despite outcome improvements due to advances in antibiotic therapy, diagnosis, and general treatment, IE results in high morbidity and mortality.³⁾

Indications for surgery in IE have continued to evolve, but frequently include intractable heart failure, abscess formation, recurrent embolic events, organism involved, and presence of prosthetic material.^{4–9)} While mortality

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has improved from 30% to 15% over the past two decades, it remains substantial.¹⁾

With increasing numbers of patients with indications for IE surgery, the identification of preoperative variables that may identify the highest risk patients (example as renal insufficiency) in this surgical cohort would be clinically useful. Although prior studies have evaluated clinical, microbiological, and echocardiographic predictors of patients with IE,^{10–14)} little is known about long-term outcomes of patients with renal insufficiency.

We thus sought to evaluate the impact of renal insufficiency on morbidity and mortality in patients with surgical intervention of IE.

Patients and Methods

We retrospectively reviewed all cases of IE diagnosed at Musashino Red Cross Hospital, from January 1998 to July 2009. Only patients with definite IE according to the modified Duke criteria were included.⁴⁾ During the study period, all patients with bacteremia were evaluated by infectious disease staff members. The following data were analyzed at the time of diagnosis: demographic features, predisposing heart diseases and past personal history, clinical features, the affected valves, bacteriologic diagnosis, echocardiographic studies, radiologic images, results of routine laboratory tests (including hematological value, liver and renal function, and inflammatory parameters), treatment and outcome. The study protocol was approved by the ethics board of our hospital. All patients were informed about the procedure, and they provided written confirmation for the operation.

The indications for surgery in IE included intractable heart failure, abscess formation, recurrent embolic events, and organism involved. We provided antibiotics and/or surgical intervention followed the guideline of the Japanese Circulation Society.

Cardiac event was defined as a cardiac death, re-cardiac operation, heart failure, and cerebral vascular accidents. Renal insufficiency was defined as patients with hemodialysis or creatinine >1.5 mg/dl.

All patients were divided two groups; one group comprised patients without renal insufficiency (group N), the other, those with renal insufficiency (group R). The following data of the two groups were compared to evaluate predictors of morbidity and mortality in patients with IE.

Indications for surgical intervention included new, severe valvular regurgitation with heart failure, intracardiac abscesses, and recurrent embolic events. However, we ex-

Table 1 Surgical intervention for infective endocarditis

Operation	Patient number
AVR	9
MVR	9
AVR + MVR	6
TVR	4
MVP	2
AVR + TVR	1
AVR + PDA closure	1
re-AVR	1
re-MVR	1
MVR + TAP	1
MVR + TVR	1
MVR + VSD closure	1
VSD closure	1

AVR: aortic valve replacement; MVR: mitral valve replacement; TVR: tricuspid valve replacement; MVP: mitral valve plasty; PDA: patent ductus arteriosus; TAP: tricuspid valve annuloplasty; VSD: ventricular septal defect

cluded patients with consciousness dysfunction from surgical indication.

Continuous data are expressed as mean $\pm$ SD with ranges when appropriate. Comparisons between two categories variables were made using the Student's *t* test for continuous variables. Otherwise, non-parametric Mann-Whitney *U* test was used. Parametric data were examined with contingency tables, with Fisher's exact test, as appropriate. The follow-up survival was assessed using the Kaplan-Meier survival curve and log rank test. Differences were considered significant at $p < 0.05$. Statistical analysis was performed with StatView for Windows version 6.0 (SAS Institute Inc, Cary, NC).

Results

During the study period, there were 71 patients with diagnosis of IE as defined by the modified Duke criteria. Of all, the 38 patients (25 males and 13 females, mean age 57.3 ± 15.2 years, range 23–83 years) were performed surgical intervention during their initial hospitalization, and the operations were shown in **Table 1**. Mean length of operation from diagnosis was 13.4 ± 12.7 days (range 1–52 days).

All patients were divided two groups; one comprised patients without renal insufficiency (N group, $n = 28$); the other, those with renal insufficiency (R group, $n = 10$).

Demographic characteristics

The characteristics at hospital arrival were shown in

Table 2 Demographic characteristics of 38 patients with infective endocarditis

	N group n = 28	R group n = 10	p value
Demographic variables			
Female	11 (39.3%)	2 (20.0%)	0.2822
Age (years)	54.1 ± 15.4	66.3 ± 10.6	0.0268
Diabetes mellitus	2 (7.1%)	1 (10.0%)	0.7809
Immunosuppressores	0 (5.0%)	1 (10.0%)	0.0946
Embolic event	16 (57.1%)	5 (50.0%)	0.7059
Laboratory data at hospital arrival			
Leukocyte (/mm ³)	11492 ± 5178	11790 ± 5015	0.8766
Hemoglobin (g/dl)	10.3 ± 2.5	8.4 ± 0.9	0.0215
CRP (mg/dl)	10.2 ± 8.9	10.8 ± 8.2	0.8504
Cre (mg/dl)	0.80 ± 0.26	2.78 ± 1.42	<0.0001
Valve involvement	13 (46.4%)	5 (50.0%)	0.8511
Aortic	16 (57.1%)	6 (60.0%)	0.8793
Mitral	4 (14.3%)	3 (30.0%)	0.2836
Tricuspid	3 (10.7%)	0 (0.0%)	0.2934
Congenital cardiac disease	2 (7.1%)	0 (0.0%)	0.3989
Prosthetic Valve			
Echocardiogram	71.7 ± 10.3	75.1 ± 13.4	0.6151
LVEF			
Outcome	0 (0.0%)	2 (20.0%)	0.0143
Hospital death	55.4 ± 31.4	55.7 ± 23.2	0.9776
Hospital stay (days)			
Microorganism			
Gram-positive	11 (39.3%)	6 (60.0%)	0.2703
Staphylococcus	9 (32.1%)	1 (10.0%)	0.1815
Streptococcus	0 (0.0%)	0 (0.0%)	
Gram-negative	3 (10.7%)	2 (20.0%)	0.3278
Other microorganisms	5 (17.9%)	1 (10.0%)	0.571
Culture negative			

CRP: C-reactive protein; LVEF: left ventricular ejection fraction

Table 2. Of all patients, the majority (94.7%) were diagnosed with native valve endocarditis. Patients in group R were significantly older than those in group N (66.3 ± 10.6: 54.1 ± 15.4 years, $p = 0.0268$). Diabetes mellitus and immunosuppressores were not different in the both groups. Though patients with an embolic event were 55.3% ($n = 21$) of all, there was no difference between both groups.

At hospital arrival, the mean hemoglobin value of group R was lower than that of group N (8.4 g/dL ± 0.9 vs. 10.3 g/dL ± 2.5, $p = 0.0215$), but the inflammatory examination (leukocyte, CRP) was not different in both groups.

There was no difference in valve involvement. Prosthetic valve infection was two patients (5.3%). Then, left ventricular function was not different between two groups, too.

There were 2 hospital deaths (5.3%) in all patients, and two patients were in group R. One was sepsis, and the other was multiple organ failure. Hospital death was more

in group R than in group N (20.0% vs. 0.0%, $p = 0.0143$). The hospital stay of all patients was a mean of 55.5 ± 29.1 days.

Organisms isolated from 38 patients is shown in **Table 3**. The majority of patients (27 patients, 71.1%) were isolated Gram-positive microorganism, and culture negative was in 6 patients (15.8%). There was no negative microorganism isolated in this study.

Long-term evaluation

Follow-up was completed in 37 patients (97.3%). The average follow-up period was 37.4 ± 33.3 months (range 2 to 139 months). With the exclusion of hospital deaths, two patients of all died, and both causes of death were cerebral bleeding at 11 months and 35 months after their hospital discharge.

Survival rates (including hospital death) by Kaplan-Meier curve are shown in **Fig. 1**. In group N, the 1, 5, 8-year survivals were 96.4%, 96.4%, and 96.4%. In

Table 3 Hazard ratio for total population, according to long-term outcome

Characteristics for survival	Odds ratio	95% confidence intervals	p value
Over 70 year old	2.954	0.267–32.627	0.3768
Female	1.535	0.160 – 14.757	0.7108
Renal insufficiency	12.104	1.349–108.641	0.0259
Aortic valve infection	1.761	0.293–10.579	0.536
Mitral valve infection	0.153	0.017–1.374	0.0936
Embolic event	0.178	0.020–1.600	0.1232
Staphylococcus infection	1.787	0.297–10.753	0.5261

Characteristics for cardiac event	Odds ratio	95% confidence intervals	p value
Over 70 year old	4.117	0.684–24.778	0.1223
Female	2.102	0.441–10.021	0.3513
Renal insufficiency	10.54	2.173–51.129	0.0035
Aortic valve infection	1.14	0.328–3.958	0.8367
Mitral valve infection	0.988	0.277–3.254	0.9856
Embolic event	0.644	0.184–2.253	0.4912
Staphylococcus infection	1.507	0.413–5.494	0.5345

Fig. 1 Actuarial survival rates estimated by Kaplan-Meier analysis. **Fig. 2** Actuarial cardiac-related event-free survival rates estimated by Kaplan-Meier analysis.

contrast, the 1, 5, 8-year survivals were 66.7%, 50.0%, and 50.0% in group R. Survival was significantly worse in group R than in group N (log rank test, $p = 0.0042$).

Then, the cardiac event-free rate by the Kaplan-Meier curve is shown in **Fig. 2**. In group N, the 1, 5, 8-year cardiac event-free rates were 96.4%, 80.4%, and 60.3%. On the other hand, the 1, 5, 8-year cardiac event-free rate were 56.0%, 42.0%, and 0.0% in group R. The actuarial freedom from cardiac events was significantly worse in

group R than in group N (log rank test: $p = 0.0003$), too.

Predictors of cardiac event

We investigated whether perioperative factors were predictors of long-term survival by multivariable analysis. **Table 3** shows the Hazard ratio of long-term survival. Only renal insufficiency (odds ratio 12.104, 95% confidence interval 1.349–108.641; $p = 0.0259$) was indicated predictors of long-term survival in patients with surgical

intervention of IE.

In the same way, we investigated predictors of cardiac event by multivariable analysis. **Table 3** shows the hazard ratio for the cardiac event. Similarly, renal insufficiency was a unique predictor of the cardiac event (odds ratio 10.540, 95% confidence interval 2.173–51.129; $p = 0.0035$).

For both survival and the cardiac event, renal insufficiency was significantly associated with the long-term evaluation.

Discussion

In the present study, we have shown that the survival rate and cardiac-event free rate were fully satisfied and that renal insufficiency was associated with high mortality and morbidity in patients with surgical intervention of IE.

Recent uncontrolled observational studies have suggested that early surgery is more beneficial for patients with IE compared with medical therapy alone.^{11,15,16} Thus, surgery is currently performed in at least 25% of patients with active IE¹² and in 50% of patients, respectively, in another study.¹⁷ In our study, cardiac surgery was performed in 53.5% of all patients with IE. The hospital death rate was 5.3% in patients who had a surgical intervention during their initial hospitalization, though the hospital death rate was 24.2% in patients who did not have a surgical intervention (data not shown).

Hoen and colleagues¹⁸ suggested that the decrease in the rate of in-hospital mortality observed in a 10-year interval may have been related to a higher rate of cardiac surgery. In a recent large prospective study including 267 patients with left side IE¹² as in other previous series^{8, 19–21} early cardiac surgery was not associated with lower in-hospital mortality. Decisions about surgery are often problematic owing to the lack of evidence from randomized controlled studies. In most cases, through consultation between the medical and the surgical teams is necessary to analyze the best strategy. Surgery in our study was performed according to conventional guidelines, predominantly in the presence of complications. However, Vikram and colleagues¹⁷ found that, in patients with left-side complicated IE, surgery was an independent predictor of 6-month survival. Reduced mortality related to surgery was particularly significant among patients with congestive heart failure. In the current study, early surgery in *Staphylococcus aureus* IE was associated with reduced in-hospital mortality in a univariate model with a

trend in multivariate analysis toward reduction of in-hospital mortality ($p = 0.1$). Moreover, early surgery was independently related to a reduction in overall mortality.

Renal insufficiency in our study was found to be a prognostic factor associated with higher mortality and morbidity rates. A number of theories about the mechanisms for increased mortality and morbidity among renal failure patients have been proposed. Dialysis-dependent renal failure patients are an immune compromised population, and this may contribute to their increased risk of postoperative infection. For example, dialysis-dependent renal failure patients have a higher wound infection rate after a lower extremity bypass.²² Whether increased infection rates are due to uremia, diabetes, steroid use secondary to autoimmune causes of renal failure, and other variables that are known to increase the risk of infection is unknown. Dialysis patients are also chronically anemic from the loss of erythropoietin production by the kidneys,^{23,24} and anemia has been shown to be associated with increased risks of mortality among patients with coronary artery bypass grafting.²⁵ Platelet dysfunction and coagulation defects from uremia are cited as mechanisms for increased bleeding among patients on dialysis,²⁶ and renal failure may serve as a marker for generalized arteriosclerosis predisposing to thromboembolic events and stroke,²⁷ as well as to less adequate revascularization and development of postoperative low-output syndrome.²⁸ In this study, preoperative hemoglobin in patients with renal insufficiency was lower than in patients without renal insufficiency (**Table 2**), and we expected that anemia-induced renal insufficiency might be one of factors affected short- and long-term outcomes.

Study limitations

The results of this study should be interpreted in light of certain limitations. Firstly, ours is a retrospective study. Nevertheless, we believe that the prevalence of IE was below the true rate, due to the retrospective nature of this study. Secondly, the present study was a single-center experience, and, as a result, was limited by the relatively small number of patients. Despite these limitations, our study provides predictors of long-term outcomes in patients with IE.

Conclusion

This study shows that renal insufficiency may allow for long-term risk stratification of patients with surgical intervention of IE.

Disclosure Statement

We report no conflicts of interest.

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