Predictors of In-hospital Mortality in Patients with Infective Endocarditis

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Abstract

Background: Infective endocarditis is a serious septic disease, and the epidemiological profile has changed over the last decade. However, there is a paucity of data regarding the current outcome and predictor of in-hospital mortality in patients with infective endocarditis.

Methods: Consecutive patients diagnosed as infective endocarditis based on the modified Duke criteria at Kansai Medical University hospital from January 2006 to June 2019 were prospectively included. The primary outcome was in-hospital mortality. Cox proportional hazards modeling was used to assess risk factors of in-hospital mortality.

Results: Of 137 consecutive patients with infective endocarditis (age 60 ±17 years-old, 62% men, 65% underlying cardiac disease, 11% chronic hemodialysis), 18 (13%) died during a hospitalization. Age and sex were not associated with in-hospital mortality. Patients on chronic hemodialysis exhibited significantly higher in-hospital mortality rate than those without (47% vs. 9%). After adjusting for comorbidities in a multivariate Cox proportional hazards model, chronic hemodialysis was a significant predictor of in-hospital mortality [hazard ratio (HR) 4.22, 95% confidential interval (CI) 1.49-12.0, $P<0.01$], independently of C-reactive protein (per 1 mg/dl; HR 1.07, 95%CI 1.02-1.12, $P<0.05$).

Conclusions: Infective endocarditis in patients on chronic hemodialysis is a serious life-threatening condition that requires an early diagnosis and an effective therapeutic approach.

Key words: infective endocarditis, mortality, chronic hemodialysis, risk factors.

Introduction

Recent advances in the care of patients with infective endocarditis include improved diagnostic capability with the use of echocardiography[1, 2] and more accurate diagnostic criteria[3]. Despite these advances, the mortality data from the cohort studies in the world wide in patients with infective endocarditis remains high, with in-hospital mortality rates in the contemporary era of nearly 20%[4, 5]. It was also reported that the epidemiological profile of infective endocarditis has changed over the last decade[2]. Chronic hemodialysis has been recognized as a risk factor for the development of infective endocarditis[6], and the number of patients on chronic hemodialysis has been increasing in Japan[7]. However, there is a paucity of data regarding the current outcome and predictors of in-hospital mortality in patients with infective endocarditis. The aim of the present study was to describe the clinical characteristics, and risk for in-hospital mortality in patients with infective endocarditis over a current 10-year period in Japan.

Methods

Study Patient

Consecutive patients diagnosed as infective endocarditis based on the modified Duke Criteria[3] at Kansai Medical University Hospital from January 2006 to June 2019 were prospectively included. Written informed consent was obtained from all participating patients, as required by the institutional review board under an approved protocol. The privacy rights of human subjects must always be observed.

Data Collections

Baseline clinical characteristics, basic cardiac condition, microbiological profile, echocardiographic findings, complications, surgical intervention and clinical outcome were obtained. The same definitions and criteria were used for all patients throughout the study

periods.

Baseline Characteristics

Clinical characteristics included age, sex, laboratory values at the time of hospital admission (white blood cell count, hemoglobin, creatinine and C-reactive protein) and comorbidities (prior infective endocarditis, diabetes mellitus, hypertension, chronic kidney disease, chronic hemodialysis, history of malignancy and auto immune disease). Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dl, a random glucose level ≥200 mg/dl, or the use of insulin or medication for diabetes. Hypertension was defined as systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg on ≥2 occasions that was not associated with acute illness or injury, or the use of antihypertensive therapy. Chronic kidney disease was defined as either kidney damage or glomerular filtration rate <60mL/min/1.73m^2 for more than 3 months. Patients who developed acute renal failure and required temporary hemodialysis during an episode of infective endocarditis were not defined as chronic hemodialysis[8].

Basic Cardiac Condition

Basic cardiac condition included underlying valvular heart disease, congenital heart disease, cardiac device implantation and history of cardiac surgery.

Echocardiography

Transthoracic echocardiography (TTE) was performed to determine location of visible vegetation, type of valve infected, the mechanism and hemodynamic severity of the valve lesion, and assessment of underlying left and right ventricular function. Transesophageal echocardiography (TEE) was performed to examine in detail (i.e. valvular perforation, annular abscess etc.) or if patients with high likelihood of infective endocarditis but negative TTE examination. Significant valvular heart disease was defined as more than moderate degree.

Complications

Complications included congestive heart failure, intracranial complication and other left- or right- side embolization due to infective endocarditis. Congestive heart failure was defined according to congestion and/or edema[9]. Intracranial complication included any hemorrhage and infarction. To identify these complications, whole-body computed tomography and/or magnetic resonance imaging examination was done at admission, if patient has no contraindication. Disseminated intravascular coagulation was defined as thrombocytopenia with elevated D-dimer or fibrin split products in the absence of significant liver disease.

Surgical Intervention

Indication and timing of surgical intervention were decided according to the guideline[10-12]. Emergent surgery was defined as surgical intervention within 24 hours from admission. Urgent surgery was defined as surgical intervention within 7 days from admission.

In-hospital Mortality

In-hospital mortality was defined as death during the hospitalization for infective endocarditis.

Statistical Analysis

Baseline characteristics were summarized in terms of mean value and standard deviation for continuous variables, or frequency numbers and % for categorical variables. Age and sex adjusted Cox proportional-hazards models were used to adjust for the effect of differences in baseline characteristics or pertinent covariates on in-hospital mortality. Within the weighted proportional hazards framework, surgical intervention was analyzed as time-dependent variables to determine the effect of surgery on in-hospital mortality[13]. We estimated univariable models as well as multivariable models, and hazard ratios (HR) and their relatives 95% confidence intervals (CI) were derived. The Kaplan-Meier method

tested for differences in the event-free rate between patients with and without chronic hemodialysis by the log-rank test, and the cumulative event-free survival curves were depicted graphically. All statistics analyses were performed using the IBM SPSS Statistics software version 24.0 (SPSS Inc., IBM, Somers, New York, USA). *P*-value<0.05 was considered statistically significant in all tests of significance.

Results

Between January 2006 and June 2019, 137 consecutive patients (mean age 60 ± 17 years, 85 men) were diagnosed infective endocarditis based the modified Duke criteria and included in this study. The mean duration of symptoms before hospital admission was 34 ± 45 days. The duration of hospital stays ranged from 1 to 264 days, with a mean of 54 ± 38 days. The baseline characteristics are shown in Table 1. Majority of patients (124 patients, 90%) had native valve endocarditis. Patients with prior infective endocarditis and on chronic hemodialysis were 11 patients (8%) and 15 patients (11%), respectively.

Basic Cardiac Condition

Of 137 patients, underlying cardiac disease was found in 89 patients (65%). Majority of underlying cardiac disease was valvular heart disease (75 patients, 55%). Among the underlying valvular heart disease, mitral valve disease was the leading cause (42 patients, 31%). Congenital heart disease and history of cardiac device implantation were found in 7 patients (5.1%), and 6 patients (4.4%), respectively.

Microbiological Profile

Blood cultures were positive in 98 patients (72%). Streptococcus (44 patients, 32%) were the most common pathogens isolated, followed by Staphylococcus in 42 patients (31%), and methicillin resistant *Staphylococcus aureus* (MRSA) was found in 13 patients (9.5%).

Echocardiographic Findings

TTE was performed in all study patients, and TEE was performed in 73 patients (53%). Vegetation with larger than 10 mm were found in 67 patients (49%). Valvular perforation and annular abscess were found in 22 patients (16%), and 14 patients (10%), respectively. The most frequently affected valve was mitral valve (80 patients, 58%), followed by aortic valve (53 patients, 39%) and tricuspid valve (5 patients, 3.6%). Multiple valves were affected in 15 patients (11%).

Clinical Events

Clinical events are shown in Table 2. Congestive heart failure and central nervous system embolism were observed in 55 patients (40%) and 46 patients (34%), respectively. Extra-cerebral embolism (i.e. coronary, renal and lower limb embolism) was detected in 17 patients (12 %). Meningitis and disseminated intravascular coagulation occurred in 9 patients (6.6%) and 19 patients (14%), respectively.

Surgical Intervention

Surgery was performed in 85 patients (62%). Mean duration from the date of admission to surgical intervention was 19 ± 21 days. Of whom, emergent surgery and urgent surgery were done in 13 and 18 patients. Reasons of emergent or urgent surgical intervention were uncontrollable heart failure (15 patients), repetitive embolization (13 patients), and uncontrollable infection (8 patients).

In-hospital Mortality

For the entire cohort, 18 patients died during a hospitalization, and the in-hospital mortality rate was 13%. The leading causes of death were heart failure in 7 patients (38%), followed by infective endocarditis related sepsis in 5 patients (28%), intracranial hemorrhage in 3 patients (17%) and pneumonia in 3 patients (17%). Table 3 shows the univariable analyses for prediction of in-hospital mortality. The factors associated with in-hospital

mortality were white blood cell count, Creatinine, C- reactive protein at admission, diabetes mellitus, hypertension, chronic kidney disease, chronic hemodialysis, MRSA infection. Surgical intervention was not associated with in-hospital mortality (P=0.68). In multivariable model for prediction of in-hospital mortality (Table 3), chronic hemodialysis was a significant predictor of in-hospital mortality (HR 4.22, 95% CI 1.49-12.0, *P*<0.01), independently of C-reactive protein (per 1 mg/dl; HR 1.07, 95%CI 1.02-1.12, *P* <0.05). MRSA infection was not associated with in-hospital mortality in multivariable model. Figure 1 shows the Kaplan-Meier estimated survival stratified by hemodialysis status. There is an increase in risk of in-hospital mortality in the patients on chronic hemodialysis than those without (Log-rank *P*< 0.0001).

Clinical Characteristics of Chronic Hemodialysis Patients

Our study included 15 chronic hemodialysis patients. Of whom, all patient's vascular access was native fistula. The baseline characteristics stratified by hemodialysis status are shown in Table 4. There was no significant difference in age and sex between 2 groups. In the chronic hemodialysis patients, hemoglobin level and streptococcus infection were lower, and creatinine level, C-reactive protein level, and staphylococcus infection (especially in MRSA infection) were higher than non-hemodialysis patients.

Discussion

Our study has the following findings; 1) despite recent advances in the diagnostic and therapeutic tools including antibiotic therapy and surgical procedures, infective endocarditis continues to be associated with a high mortality rate, 2) in patients with infective endocarditis, chronic hemodialysis is an independent risk of death, predicting a 4-hold increase in in-hospital mortality.

High mortality rate in patients with infective endocarditis

In our series, overall in-hospital mortality was 13%, which is still high. Surprisingly, mortality rate was not decreased compared with that in the decade of the 1980s[14]. There are two possible explanations for this. First, the patient's characteristics changed dramatically. In a previous study in Japan published in 1980[15], most of the patients with infective endocarditis were aged in their 20 s and 30 s and rheumatic heart disease was the major risk factor of infective endocarditis. On the other hands, the average age in our study was 60 years old, and it was similar to other recent cohort studies[13, 16], and patients with rheumatic heart disease were rarely seen due to effective prevention and treatment of streptococcal infections in recent years. At the present time, major risk factors for infective endocarditis are compromised host such as advanced age, chronic hemodialysis, immunosuppression, diabetes, cancer and intravenous drug use[5, 17, 18]. Especially, the number of patients on chronic hemodialysis continues to increase up to now from the 1960s in Japan[7]. Second, microbiological profile has also changed. Previous studies reported that staphylococcal infective endocarditis was independently associated with in-hospital mortality[13]. Staphylococcus is a well-known cause of bacteremia in immunosuppressed hosts such as chronic hemodialysis patients and diabetes mellitus. Although Streptococcus was the most common causative microbiological of infective endocarditis, percentage of Staphylococcus has been increasing[14].

Risk of In-hospital Mortality

In our study, chronic hemodialysis and high C-reactive protein were independent predictors of in-hospital mortality. Of 15 chronic hemodialysis patients in our study, 7 patients (47%) died during hospital admission, and chronic hemodialysis was associated with 4-fold increase in risk for in-hospital mortality, independently of other comorbidities. In chronic hemodialysis patients, MRSA infection was higher than in the non-hemodialysis patients, and three out of seven patients who died were MRSA infection. MRSA infection in chronic

hemodialysis patients is a very important issue, but this study is relatively small, so further investigation is needed.

Oun et al. reported an observational study consisted of 29 chronic hemodialysis patients who were diagnosed as an infective endocarditis[19]. In this previous study reported that in-hospital mortality rate was 37.9%, which was extremely higher than other observational study. They concluded that damaged, or typically calcified valves are associated with higher incidence of infective endocarditis in chronic hemodialysis patients and the prevention of ectopic cardiac and valvular calcification should be considered a priority[19]. Moreover, vascular access was often suspected to a portal of infection. Doulton et al. reported that native fistula of vascular access should not be overlooked as a possible source of bacteremia in infective endocarditis, even if there is a no visible sign of infection[20].

In our study, there was no difference in the surgical intervention rate between the chronic hemodialysis patients and the non-hemodialysis patients, and surgery was not a negative independent predictor for in-hospital mortality, and Jones et al. also reported same results[21]. Therefore, early detection, close monitoring by blood cultures and aggressive antibiotic treatment are needed in such patients. The most important fact may be meticulous care of vascular access to prevent incidence of infective endocarditis.

C-reactive protein was also an important risk factor to predict in-hospital mortality in patients with infective endocarditis, which has not been regarded as an independent risk factor in previous researches. Some researchers show that mean C-reactive protein concentration is significantly higher in patients who died during hospital admission in infective endocarditis[2]. Higher C-reactive protein means that it is difficult to control infection, leading to exhaustion. Therefore, to determine the causative bacteria and to appropriately use the effective antibiotics is important to reduce in-hospital mortality in infective endocarditis patients.

Limitations

Our study has some limitations. First, this study is a single-center study and a total number of patient was relatively small. Study with a larger number of patients and multicentric studies are warranted to investigate. Second, it is an observational study, so selection bias for surgical intervention or medical treatment might be present, although our treatments were selected based on the recommended guidelines[10-12, 22]. Finally, hemodialysis duration was not considered in our study.

Conclusions

In patients with infective endocarditis, in-hospital mortality was still high, especially in patients on chronic hemodialysis. Further studies are warranted to improve the prognosis of infective endocarditis patients on chronic hemodialysis.

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Disclosures

We have no conflicts of interest to disclose.

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Figure Legends

Figure 1.

Kaplan-Meier estimates of cumulative survival in patients with chronic hemodialysis compared with those without.

Table 1. Baseline characteristics

Variables	All patients (n=137)	Survived (n=119)	Died (n=18)
Clinical			
Age (years)	60 ± 17	59 ± 18	64 ± 13
Male gender	85 (62)	75 (63)	10 (56)
White blood cell count (×10^3/μl)	11.9 ± 7.1	11.3 ± 6.3	15.6 ± 10.1
Hemoglobin (g/dl)	10.8 ± 2.0	10.8 ± 2.0	10.4 ± 2.1
Creatinine (mg/dl)	1.60 ± 2.28	1.44 ± 2.15	2.69 ± 2.86
C-reactive protein (mg/dl)	9.5 ± 8.4	8.5 ± 7.8	16.6 ± 8.9*
Native valve endocarditis	124 (90)	111 (93)	13 (72)*
Prior infective endocarditis	11 (8.0)	10 (8.4)	1 (5.6)
Diabetes mellitus	24 (18)	18 (15)	6 (33)
Hypertension	48 (35)	37 (31)	11 (61)*
Chronic kidney disease	56 (41)	42 (35)	14 (78)*
Chronic hemodialysis	15 (11)	8 (6.7)	7 (39)*
History of malignancy	18 (13)	14 (12)	4 (22)
History of auto immune disease	6 (4.4)	5 (4.2)	1 (5.6)
Basic Cardiac Condition			
Underlying cardiac disease	89 (65)	79 (66)	10 (56)
Underlying valvular heart disease	75 (55)	66 (55)	9 (50)
Mitral valve	42 (31)	37 (31)	5 (28)
Aortic valve	37 (27)	33 (28)	4 (22)
Congenital heart disease	7 (5.1)	6 (5.0)	1 (5.6)
Cardiac device implantation	6 (4.4)	6 (5.0)	0 (0)

Table 1. Baseline characteristics (continue)

Variables	All patients (n=137)	Survived (n=119)	Died (n=18)
History of cardiac surgery	26 (19)	21 (18)	5 (28)
Microbiological profile			
Positive cultures	98 (72)	86 (72)	12 (67)
Streptococcus	44 (32)	42 (35)	2 (11)
Mitis group Streptococcus	22 (16)	22 (18)	0 (0)
Other Streptococcus	22 (16)	20 (17)	2 (11)
Staphylococcus	42 (31)	33 (28)	9 (50)
MSSA	17 (12)	15 (13)	2 (11)
MRSA	13 (9.5)	8 (6.7)	5 (28)*
CNS	4 (2.9)	3 (2.5)	1 (5.6)
Others	12 (8.8)	11 (9.2)	1 (5.6)
Echocardiography			
Large vegetation (>10mm)	67 (49)	59 (50)	8 (44)
Perforation	22 (16)	21 (18)	1 (5.6)
Abscess	14 (10)	10 (8.4)	4 (22)
Location of the infection			
Mitral valve	80 (58)	69 (58)	11 (61)
Mitral native valve	74 (54)	65 (55)	9 (50)
Mitral prosthetic valve	6 (4.4)	4 (3.4)	2 (11)
Aortic valve	53 (39)	44 (37)	9 (50)
Aortic native valve	45 (33)	39 (33)	6 (33)
Aortic prosthetic valve	8 (5.8)	5 (4.2)	3 (17)

Table 1. Baseline characteristics (continue)

Variables	All patients (n=137)	Survived (n=119)	Died (n=18)
Tricuspid valve	5 (3.6)	4 (3.4)	1 (5.6)
Pulmonary valve	3 (2.2)	3 (2.5)	0 (0)
Intracardiac device	2 (1.5)	2 (1.7)	0 (0)

Values are given as mean± SD or number (%).

Differences were evaluated with Chi-square analyses (categorical variables) and 2-sample *t* tests (continuous variables).

CNS: Coagulase-negative *Staphylococcus*, MRSA: Methicillin-resistant *Staphylococcus aureus,* MSSA: Methicillin-sensitive *Staphylococcus aureus.*

**P* <0.05 versus patients who survived.

Table 2. Clinical events and outcomes

Outcomes	n (%)
Heart failure	55 (40)
Embolism	65 (47)
Left side embolism	63 (46)
Central nervous system embolism	46 (34)
Extra-cerebral embolism	17 (12)
Coronary embolism	2 (1.5)
Renal embolism	5 (3.6)
Lower limb embolism	11 (8.0)
Right side embolism	4 (2.9)
Cerebral hemorrhage	17 (12)
Meningitis	9 (6.6)
Disseminated intravascular coagulation	19 (14)
Surgical intervention	85 (62)
In-hospital mortality	18 (13)

Table 3. Univariable and multivariable model for prediction of in-hospital mortality

Variables	Univariable		Multivariable	
	HR (95% CI)	*P* Value*	Adjusted HR (95% CI)	*P* Value
Clinical				
Age (per 10 years)	1.18 (0.89-1.58)	0.24		
Male gender	0.73 (0.29-1.86)	0.52		
White blood cell count (per 10^3/μl)	1.07 (1.02-1.12)	<0.05		
Hemoglobin (per 1 g/dl)	0.94 (0.74-1.19)	0.59		
Creatinine (per 1 mg/dl)	1.18 (1.03-1.34)	<0.05		
C reactive protein (per 1 mg/dl)	1.10 (1.05-1.16)	<0.001	1.07 (1.02-1.12)	<0.05
Native valve endocarditis	0.37 (0.12-1.16)	0.09		
Prior infective endocarditis	0.68 (0.09-5.13)	0.71		
Diabetes mellitus	2.94 (1.04-8.36)	<0.05		
Hypertension	3.34 (1.12-9.95)	<0.05		
Chronic kidney disease	5.82 (1.80-18.8)	<0.01		
Chronic hemodialysis	6.19 (2.37-16.2)	<0.001	4.22 (1.49-12.0)	<0.01
History of malignancy	1.90 (0.60-5.99)	0.28		
History of auto immune disease	1.10 (0.14-8.55)	0.93		
Basic Cardiac Condition				
Valvular heart disease	0.70 (0.27-1.82)	0.47		
Congenital heart disease	1.27 (0.17-9.64)	0.82		
History of cardiac surgery	1.51 (0.53-4.28)	0.44		

Table 3. Univariable and multivariable model for prediction of in-hospital mortality (continue)

Variables	Univariable		Multivariable	
	HR (95% CI)	*P* Value*	Adjusted HR (95% CI)	*P* Value
Streptococcus	0.26 (0.06-1.15)	0.08		
Staphylococcus	2.28 (0.91-5.76)	0.08		
MRSA	4.33 (1.54-12.2)	<0.01	2.03 (0.63-6.53)	0.23
Large vegetation (>10mm)	0.90 (0.35-2.30)	0.82		
Surgical intervention**	0.80 (0.27-2.34)	0.68		

*P-value: age and sex adjusted, ** time-dependent variable

CI: confident interval, CNS: Coagulase-negative *Staphylococcus,* HR: hazard ratio, MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-sensitive *Staphylococcus aureus.*

Table 4. Baseline characteristics stratified by chronic hemodialysis status

Variables	Non- hemodialysis (n=122)	Chronic hemodialysis (n=15)
Clinical		
Age (years)	59 ± 18	65 ± 10
Male gender	74 (61)	11 (73)
White blood cell count (×10^3/μl)	11.4 ± 6.5	15.3 ± 10.4
Hemoglobin (g/dl)	10.9 ± 2.0	9.4 ± 1.9*
Creatinine (mg/dl)	1.05 ± 1.41	6.07 ± 3.05*
C-reactive protein (mg/dl)	8.7 ± 7.7	16.7 ± 10.5*
Native valve endocarditis	112 (92)	12 (80)
Prior infective endocarditis	8 (6.6)	3 (20)
Diabetes mellitus	19 (16)	5 (33)
Hypertension	39 (32)	9 (60)*
Chronic kidney disease	41 (34)	15 (100)*
History of malignancy	17 (14)	1 (6.7)
History of auto immune disease	5 (4.1)	1 (7.1)
Basic Cardiac Condition		
Underlying cardiac disease	80 (66)	9 (60)
Underlying valvular heart disease	67 (55)	8 (53)
Mitral valve	37 (30)	5 (33)
Aortic valve	32 (26)	5 (33)
Congenital heart disease	7 (5.7)	0 (0)
Cardiac device implantation	6 (4.9)	0 (0)
History of cardiac surgery	21 (17)	5 (33)

Table 4. Baseline clinical characteristics stratified by chronic hemodialysis status (continue)

Variables	Non- hemodialysis (n=122)	Chronic hemodialysis (n=15)
Microbiological profile		
Positive cultures	89 (73)	9 (60)
Streptococcus	43 (35)	1 (6.7)*
Mitis group Streptococcus	22 (18)	0 (0)*
Other Streptococcus	21 (17)	1 (6.7)*
Staphylococcus	34 (28)	8 (53)*
MSSA	16 (13)	1 (6.7)
MRSA	8 (6.6)	5 (33)*
CNS	3 (2.5)	1 (6.7)
Others	12 (10)	0 (0)
Echocardiography		
Large vegetation (>10mm)	57 (47)	10 (67)
Perforation	20 (16)	2 (13)
Abscess	13 (11)	1 (6.7)
Location of the infection		
Mitral valve	69 (57)	11 (73)
Mitral native valve	65 (53)	9 (60)
Mitral prosthetic valve	4 (3.3)	2 (13)
Aortic valve	47 (39)	6 (40)
Aortic native valve	41 (34)	4 (27)
Aortic prosthetic valve	6 (4.9)	2 (13)

Table 4. Baseline clinical characteristics stratified by chronic hemodialysis status (continue)

Variables	Non- hemodialysis (n=122)	Chronic hemodialysis (n=15)
Tricuspid valve	4 (3.3)	1 (6.7)
Pulmonary valve	3 (2.5)	0 (0)
Intracardiac device	2 (1.6)	0 (0)

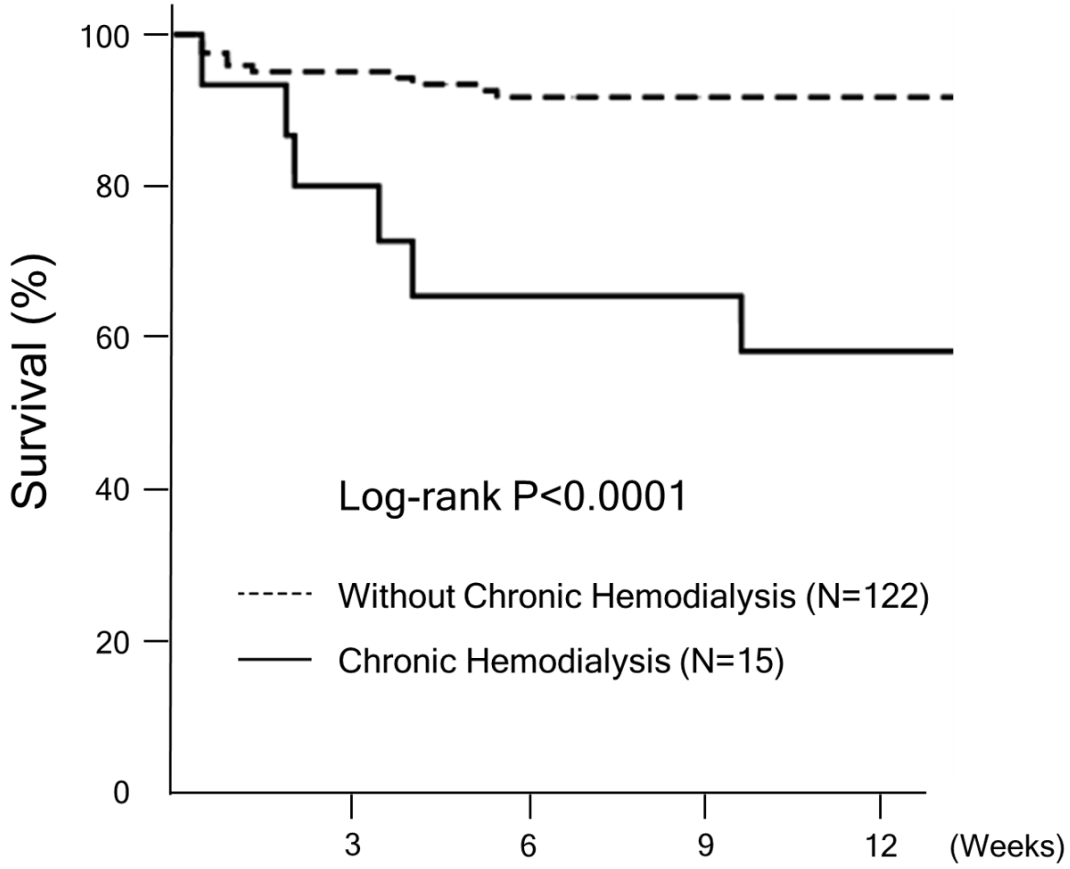
Values are given as mean± SD or number (%).

Differences were evaluated with Chi-square analyses (categorical variables) and 2-sample *t* tests (continuous variables).

CNS: Coagulase-negative *Staphylococcus*, MRSA: Methicillin-resistant *Staphylococcus aureus,* MSSA: Methicillin-sensitive *Staphylococcus aureus.*

*P <0.05 versus patients who non-hemodialysis.

Figure 1.


100
80
60
40
20
0
Survival (%)
Log-rank P<0.0001
Without Chronic Hemodialysis (N=122)
Chronic Hemodialysis (N=15)
3
6
9
12
(Weeks)