



Surgical Outcomes for Native Valve Endocarditis

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Background: The aim of this study was to evaluate the short-term and long-term results of surgical treatment for native valve endocarditis (NVE) and to investigate the risk factors associated with mortality.

Methods: Data including patients' characteristics, operative findings, postoperative results, and survival indices were retrospectively obtained from Hallym University Sacred Heart Hospital.

Results: A total of 29 patients underwent surgery for NVE (affecting the mitral valve in 20 patients and the aortic valve in 9) between 2003 and 2017. During the follow-up period (median, 46.9 months; interquartile range, 19.1–107.0 months), the 5-year survival rate was 77.2%. In logistic regression analysis, body mass index ($p=0.031$; odds ratio [OR], 0.574; 95% confidence interval [CI], 0.346–0.951), end-stage renal disease (ESRD) ($p=0.026$; OR, 24.0; 95% CI, 1.459–394.8), and urgent surgery ($p=0.010$; OR, 34.5; 95% CI, 2.353–505.7) were significantly associated with in-hospital mortality. Based on Cox proportional hazard regression analysis, the statistically significant predictors of long-term outcomes were hypertension, ESRD, and urgent surgery.

Conclusion: Surgical treatment for NVE is associated with considerable mortality. The in-hospital mortality and 5-year survival rates of this study were 13.8% and 77.2%, respectively. Underlying conditions, including hypertension and ESRD, and urgent surgery were independent risk factors for unfavorable outcomes.

Keywords: Endocarditis, Surgery, Outcomes, Heart valve disease, Risk factors

Introduction

Infective endocarditis (IE) has considerable morbidity and mortality rates, and about half of all patients require surgical treatment. Despite therapeutic advances, the 1-year mortality of IE remains high, at 40% [1].

Various risk factors, such as the patient's underlying disease (including prosthetic valve endocarditis), complications of IE, the causative infectious organism, and echocardiographic findings, are associated with the clinical outcomes of patients with IE. Surgical timing is also a significant predictor of mortality and morbidity in IE cases [2-4].

Recently, the increased use of prosthetic valves has led to changes in the potential causative organisms underlying IE. However, prosthetic valve endocarditis was excluded from this study due to differences in its prognosis compared to native valve endocarditis (NVE). We hypothesized

that certain risk factors for NVE, including the underlying disease, oral hygiene, intracardiac involvement, preoperative embolic events, the infectious organism, and surgical timing, would be associated with survival.

In the present study, we aimed to retrospectively evaluate the short-term and long-term results of surgical treatment for NVE and to investigate the risk factors associated with mortality.

Methods

Study subjects

Between March 2003 and February 2017, 29 consecutive patients underwent surgical treatment for NVE at Hallym University Sacred Heart Hospital. The median follow-up period was 46.9 months (interquartile range [IQR], 19.1–



107.0 months), with full patient compliance. Data including patient characteristics, operative findings, postoperative results, and survival indices for the surgical treatment of NVE were retrospectively obtained from our institution's database. The institutional review board of Hallym University Sacred Heart Hospital approved this study without requiring informed consent (IRB approval no., 2017-I109).

Institutional strategies for infective endocarditis

Each patient underwent both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). In all cases except those requiring urgent surgical intervention, follow-up TEE or TTE was performed after completion of conventionally recommended antibiotics treatment. Brain and abdominal imaging study conducted for all patients to find embolic infarction during admission. Consultation to dental department for evaluating oral hygiene status was done to prevent further IE. To determine the regimen of antibiotic treatment for each patient, infectious disease specialists provided suggestions and recommendations on the type of drug, period of treatment, and possible side effects.

Surgical procedure

For routine cardiovascular anesthesia and monitoring techniques, including Swan-Ganz catheterization, median sternotomy was performed to all patients by a single surgeon. After the sternotomy, a cardiopulmonary bypass (CPB) was initiated with moderate systemic hypothermia (34°C). Histidine-tryptophan-ketoglutarate solution (Custodiol; Essential Pharmaceuticals LLC, Durham, NC, USA) was routinely used for cardiac arrest in antegrade or retrograde fashion. Mitral valve surgery was typically performed via a transseptal approach followed by right atriotomy, while the aortic valve operation was conducted by aortotomy. After removal of the infected tissue, including the valve, replacement or repair of the valve was performed. The anesthesiologist intraoperatively confirmed valve movement and leakage using TEE. After weaning off CPB, the sternum was closed with wires and plates.

Clinical outcomes

Early mortality was defined as either occurring in-hospital or within 30 days of surgery. Postoperative morbidity was recorded as follows. Postoperative bleeding and paravalvular leakage were considered to be present in cases re-

quiring reoperation. Low cardiac output syndrome (LCOS) was defined as either a prolonged (>48 hours post-surgery) intensive care unit stay due to abnormal preload, contractility, heart rate, or afterload, or as the need to apply an intra-aortic balloon pump or veno-arterial extracorporeal membrane oxygenation. Acute renal failure was defined as renal failure requiring dialysis. A cerebrovascular accident (CVA) was considered to be present in any patient with the corresponding neurological symptoms whose condition was confirmed by brain imaging. We categorized infections as pneumonia, mediastinitis, or sepsis. Pneumonia was defined as an infection requiring ventilator care and additional antibiotics. Mediastinitis was recorded as present in cases requiring surgical intervention. If bacteremia was identified after surgery, the condition was classified as sepsis.

All cases of mortality that occurred during the follow-up period were categorized as late mortality. Late morbidity included any admission during the follow-up period except for the purpose of preoperative anticoagulation bridging.

Statistical analysis

All categorical variables were represented as absolute figures and percentages, and continuous variables were represented as mean±standard deviation. Continuous variables were compared using the Student t-test, and categorical variables were compared using the chi-square test or the Fisher exact test when the minimum expected count was less than 5. Kaplan-Meier estimates were used for the analysis of long-term survival. Univariate logistic regression was performed for the analysis of in-hospital mortality, while Cox proportional hazard regression was performed for the analysis of late mortality. Multivariate analyses were not performed due to the small sample size. All p-values below 0.05 were considered to indicate statistical significance. All statistical analyses were performed using IBM SPSS Statistics ver. 24.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

The baseline characteristics, including demographic information and preoperative findings, of the 29 patients are summarized in Table 1. The mean age of the patients was 57.1 years, and 6 patients were women. The underlying diseases in our study population were as follows: hypertension

Table 1. Patient demographics and characteristics (N=29)

Characteristic	Value
Age (yr)	57.1±0.8
Female sex	6 (20.6)
Body mass index (kg/m ²)	23.1±3.0
Hypertension	11 (37.9)
Diabetes mellitus	5 (17.2)
End-stage renal disease	3 (10.3)
Poor oral hygiene	11 (45.8)
Symptoms	
Fever	14 (48.3)
Sepsis	8 (27.6)
Dyspnea (New York Heart Association class III or IV)	12 (41.4)
Neurological	6 (20.7)
Embolic events	
Cerebrovascular accident	10 (34.5)
Peripheral	5 (17.2)
Coronary artery disease	4 (13.8)
European System for Cardiac Operative Risk Evaluation II (%)	4.0±4.8
Urgent surgery	5 (17.2)
Echocardiography	
Intracardiac involvement	
Mitral	20 (69.0)
Aortic	9 (31.0)
Vegetation	26 (89.7)
Vegetation size (mm)	14.7±6.9
Ejection fraction (%)	58.3±13.8
Microbiological findings	
<i>Streptococcus</i>	14 (48.3)
<i>Staphylococcus</i>	7 (24.1)
Other	2 (6.9)
Culture-negative	6 (20.7)

Values are presented as mean±standard deviation or number (%).

in 11 patients, diabetes mellitus (DM) in 5 patients, and end-stage renal disease (ESRD) in 3 patients. All patients except 5 who required urgent surgery were examined by a dentist to assess their oral hygiene, and poor oral hygiene that required treatment was reported in 11 patients. Four patients were found to have coronary artery disease, as evidenced by coronary angiography. Mortality risk was calculated for all patients using the European System for Cardiac Operative Risk Evaluation, with a median risk of 2.2% (IQR, 1.8%–4.0%). Urgent operations were required in 5 cases, 4 to treat aggravated heart failure and 1 to treat recurrent CVA. Patients showed various symptoms, of which fever was the most common (14 of 29, 48%). The second most common symptom was dyspnea (12 of 29, 42%), followed by general weakness (8 of 29, 27%). Neurological symptoms frequently appeared alone, and the rate of such

Table 2. Operative and postoperative outcomes (N=29)

Variable	Value
Operation type	
Mitral valve replacement (mechanical, 8; tissue, 7)	15 (51.7)
Mitral valve repair	2 (6.9)
Aortic valve replacement (mechanical, 6; tissue, 2)	8 (27.6)
Double valve replacement (mechanical, 1; tissue, 1)	2 (6.9)
Mitral valve replacement with coronary artery bypass (mechanical, 1; tissue, 1)	2 (6.9)
Valve pathology	
Annular destruction	3 (10.3)
Leaflet perforation	9 (31.0)
Chordae rupture	8 (27.6)
Early outcome	
In-hospital mortality	4 (13.8)
Sepsis	5 (17.2)
Low cardiac output syndrome	2 (6.9)
Postoperative cerebrovascular accident	1 (3.4)
Gastrointestinal bleeding	2 (6.9)
Reoperation for bleeding	1 (3.4)
Tracheostomy	2 (6.9)
Ventilator care (hr)	8 (5–17)
Intensive care unit stay (day)	3 (2–3)
Late outcome	
Late mortality	2 (6.9)
Reoperation for paravalvular leak	1 (3.4)

Values are presented as number (%) or median (interquartile range).

symptoms was relatively low (6 of 29, 21%). Preoperative embolic events were divided into 2 categories: CVA in 10 patients and peripheral embolism in 5, where all 5 patients experienced asymptomatic splenic infarction.

Preoperative echocardiography showed that 20 patients had IE in the mitral valve and 9 patients in the aortic valve. A total of 26 patients had visible vegetation, and the mean size was 14.7 mm. With the exception of 2 patients with severe left ventricular dysfunction, the ejection fraction for all patients fell within the normal range, with a mean of 58.3%. The etiology of the infectious organisms was *Streptococcus* in 14 patients, *Staphylococcus* in 7, and culture-negative in 6 patients, while findings classified as “other” included *Bacillus* in 1 patient and *Enterococcus* in 1 patient.

Early outcomes

The operative and postoperative outcomes are shown in Table 2. Fifteen patients underwent mitral valve replacement, while 2 patients received mitral valve repair, including neo-chordae formation after removal of vegetation. Eight patients underwent aortic valve replacement. Two patients underwent both mitral and aortic valve replace-

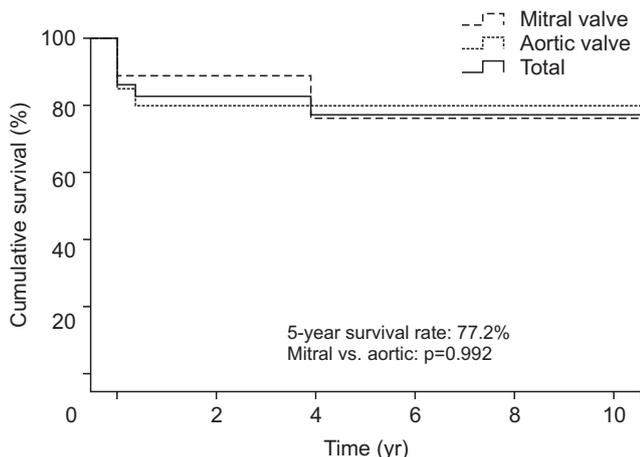


Fig. 1. Kaplan-Meier analysis in patients undergoing surgery for infective endocarditis.

ment, but the infections in these cases did not involve mitral-aortic intervalvular fibrosa. Two patients underwent concomitant coronary artery bypass and mitral valve replacement.

There were 3 major valve pathologies: annular destruction in 3 patients, leaflet perforation in 9, and chordae rupture in 8. Nevertheless, these patients did not require additional procedures for mitral-aortic intervalvular fibrosa or aortic root reconstruction.

In-hospital mortality occurred in 4 patients (4 of 29, 13.7%). Two patients died due to septic shock, one each on postoperative days 20 and 62. The first patient was relatively older (68 years) and had undergone a double valve operation. In this patient, both C-reactive protein levels and leukocyte counts were high after surgery and continued to increase. The other patient had hypertension, ESRD, and asymptomatic preoperative CVA. He was re-intubated and was given additional antibiotics to treat pneumonia. Afterwards, he suffered a new infarction along with gastrointestinal bleeding during the postoperative period.

The other 2 patients died due to LCOS on postoperative days 4 and 84. One patient underwent concomitant coronary artery bypass and mitral valve replacement. Postoperatively, inotropic agents and continuous renal replacement therapy were administered but were unsuccessful. The other patient initially showed severe heart failure and underwent an urgent operation. After surgery, he received extracorporeal membrane oxygenation, but did not survive.

Regarding complications, sepsis occurred in 5 patients, of whom 1 had methicillin-resistant *Staphylococcus aureus* as the etiology of the infection. Two patients exhibited LCOS, and both were recorded as cases of in-hospital mor-

Table 3. Univariate analysis of risk factors associated with in-hospital mortality

Risk factors for in-hospital mortality	Odds ratio (95% confidence interval)	p-value
Body mass index (kg/m ²)	0.574 (0.346–0.951)	0.031
End-stage renal disease	24.00 (1.459–394.8)	0.026
Urgent surgery	34.50 (2.353–505.7)	0.010

Table 4. Univariate analysis of risk factors associated with 5-year mortality

Risk factors for 5-year mortality	Hazard ratio (95% confidence interval)	p-value
Hypertension	10.57 (1.212–92.26)	0.033
End-stage renal disease	12.45 (2.456–63.13)	0.002
Urgent surgery	6.496 (1.288–32.77)	0.023

tality. Postoperative CVA occurred in 1 patient who showed normal brain imaging and no neurological symptoms preoperatively. Although appropriate protective agents were applied, gastrointestinal bleeding occurred in 2 patients. One patient underwent reoperation for postoperative bleeding and was discharged on the 16th postoperative day without further complications.

Late outcomes

Kaplan-Meier analysis showed that the 5-year survival rate was 77.2%, with no significant difference according to the involved valve (Fig. 1). Two patients died during the follow-up period; the cause of death was lung cancer in 1 and a traffic accident in the other. One patient had a late postoperative complication (a paravalvular leak) on postoperative day 72. He underwent reoperation for the leak and was discharged without further complications. The details of each patient's clinical course are presented in Supplemental Table 1.

Factors associated with clinical outcomes (early and late)

The results of a univariate analysis for early and late outcomes are shown in Tables 3 and 4. In logistic regression analysis, body mass index ($p=0.031$; odds ratio [OR], 0.574; 95% confidence interval [CI], 0.346–0.951), ESRD ($p=0.026$; OR, 24.0; 95% CI, 1.459–394.8), and urgent surgery ($p=0.010$; OR, 34.5; 95% CI, 2.353–505.7) were significantly associated with the risk of in-hospital mortality. In Cox proportional hazard regression analysis, the statistically sig-

nificant predictors of long-term outcome were hypertension ($p=0.033$; hazard ratio [HR], 10.57; 95% CI, 1.212–92.2), ESRD ($p=0.002$; HR, 12.45; 95% CI, 2.456–63.13), and urgent surgery ($p=0.023$; HR, 6.496; 95% CI, 1.288–32.7).

Discussion

Our retrospective study focused on risk factors associated with early and late survival based on a single-center database of surgical treatment for NVE. In logistic regression analysis, preoperative risk factors such as body mass index, ESRD, and urgent surgery appeared to increase in-hospital mortality. In our long-term survival analysis, the 5-year survival rate was 77.2%, and hypertension, ESRD, and urgent surgery were associated with long-term mortality.

Marks et al. [5] in 2015 reported that the underlying disease was not significantly correlated with survival, even if the patient had a previous history of endocarditis, valve replacement, or congenital heart disease. In contrast, the findings of the present study indicated that hypertension or ESRD significantly affected the survival of patients with NVE. Although no significant association was observed between DM and survival in this study, a previous study reported that DM was associated with the risk of in-hospital death [6].

The importance of oral hygiene in patients with IE has long been emphasized [7,8]. This study assessed whether oral hygiene affected survival. Two patients (6.8%) had undergone previous dental procedures after which they developed IE. This number is relatively small compared to those in previous studies [7,8]; however, it can be explained by the large number of patients in our study with IE of unidentified origin (14/29, 51.7%). Eleven patients (45.8%) exhibited poor oral hygiene upon dental examination. In our study, these 2 factors—oral hygiene status and dental origin as the source of IE—showed no significant impacts on survival. This is thought to be the result of oral *Streptococcus* being less harmful than other organisms. In a previous study, oral *Streptococcus* was even found to have an OR <1 for in-hospital mortality, meaning that it had a preventive effect on mortality [1].

Because the cardiopulmonary physiology differs according to the valve, the side of the IE-affected valve may also be an important risk factor. Although the subjects in this study had only left-side IE, Gaca et al. [9] in 2013 reported that the surgical results for right-side IE were similar to those for left-side IE, with both showing a 7% in-hospital mortality rate. Though Lee et al. [10] in 2014 excluded drug users from their study, their results for right-side IE were

similar to those for left-side IE. Although no study has reported a significant difference between the results of aortic valve and mitral valve endocarditis, one study showed that the postoperative results of aortic valve and mitral valve endocarditis may vary according to the underlying pathophysiology and the surgical techniques used during treatment [6]. In our study, a subgroup analysis was conducted to compare the 2 valves. Both groups were similar except with regard to the valvular pathophysiology of chordae rupture ($p=0.033$) and showed no significant difference in early mortality ($p=0.780$; OR, 1.412; 95% CI, 0.126–15.78) or long-term mortality ($p=0.992$; HR, 1.009; 95% CI, 0.182–5.582).

Embolic events causing patient non-compliance could affect postoperative care and worsen outcomes. In this study, preoperative embolic events were not significantly related to survival; however, other studies have shown contradictory results. Chu et al. [11] in 2004 showed that peripheral embolic events were significantly related to in-hospital mortality. Delahaye et al. [8] in 2007 assessed both Glasgow Coma Scale scores and cerebral hemorrhage, and both variables were reported to affect mortality. Our study included asymptomatic patients with only imaging-proven embolisms, which could explain our finding that having an embolism did not significantly affect survival.

Survival can be impacted by the microbiological etiology of the infection. Many studies have found that *S. aureus*, various species of fungi, and Gram-negative *Bacillus* were predictors of poor outcomes [1,7,8,11]. In this study, the infectious organism was *S. aureus* in 2 patients. Although poor outcomes were expected in these patients, they recovered well in-hospital and during the follow-up period, probably due to their young age and because they had no underlying disease. Further studies with a larger sample size will most likely yield different results depending on the infectious organisms present.

Surgical timing is also an important factor, as improper timing makes patient care more difficult. Urgent surgery indications mainly fall into 3 categories: heart failure aggravation, resistant organisms, and recurrent embolic events [12]. Compared with previous guidelines, the indications for urgent surgery are being gradually expanded. This trend is driven by a variety of factors, such as the development of antibiotics, the proposal of new surgical techniques, and evidence from recent studies [12]. However, the need for urgent surgery remains an unpleasant situation and may be a risk factor for poor outcomes, as shown in this study. In contrast, Kang et al. [13] in 2012 reported that urgent surgery was associated with lower rates of mortality and complications, such as stroke. This discrepancy

may be explained by the fact that our study included conventional indications of urgent operations that were excluded by Kang et al. [13]. San Román et al. [14] in 2007 reported that the decision of surgical timing was crucial and must be carefully made by the endocarditis treatment team during the active phase of the disease. We analyzed cases of delayed surgery after prolonged (>28 days) antibiotic management. Eleven patients underwent delayed surgery, 2 of whom died; however, these results were not statistically significant. Nonetheless, long-term antibiotic treatment without surgery is thought to have an effect on mortality, and further studies of this relationship are needed.

Since mechanical valves and tissue valves are known to produce no difference in survival rates [15], the valve was chosen in the same fashion as for patients undergoing normal cardiac surgery. Our study included 16 mechanical valve operations and 11 tissue valve operations. These groups (mechanical and tissue) showed no significant differences in early mortality ($p=0.162$; OR, 5.625; 95% CI, 0.500–63.28) or long-term mortality ($p=0.152$; HR, 3.465; 95% CI, 0.632–19.00).

Limitation

This study is limited by its retrospective nature and small number of patients; additionally, its evaluation of cases treated only at a single center may limit the ability to generalize the results. In addition, principally due to the limited number of patients, the statistical findings of the present study may not be valid, even for parameters with a p -value were less than 0.05. Nonetheless, this study is meaningful in that it aimed to show the characteristics of patients and surgical outcomes at a single institution.

Conclusion

Surgical treatment for NVE is associated with considerable morbidity and mortality. In our study, the 5-year survival rate was 77.2%, and several variables were found to be associated with survival. Urgent surgery and underlying ESRD showed significant correlations with both in-hospital mortality and 5-year survival. Therefore, patients with these risk factors should be closely observed to prevent unfavorable results.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary materials

Supplementary materials can be found via <https://doi.org/10.5090/kjtcvs.2020.53.1.1>. Supplemental Table 1. Details of patients undergoing surgery for infective endocarditis.

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