Diabetes mellitus adversely affects mortality and recurrence after valve surgery for infective endocarditis

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ABSTRACT

Background: Although diabetes mellitus (DM) increases the incidence of infective endocarditis (IE), little is known about the outcome of valve surgery for active IE in patients with DM. We evaluated the clinical outcomes of valve surgery for IE in patients with DM.

Methods: Between 2009 and 2016, 470 patients underwent valve surgery for definitive left-sided active IE at 12 affiliated hospitals. We compared the preoperative variables and clinical outcomes between patients without (n = 374) and with DM (n = 96).

Results: Staphylococcus and chronic hemodialysis were more prevalent in patients with DM, and these patients had greater preoperative inflammation levels and worse renal function than patients without DM. In-hospital mortality was 8% in patients without DM and 13% in patients with DM ($P = .187$). The overall survival rate at 1 and 5 years was 87% and 81% in patients without DM and 72% and 59% in patients with DM ($P < .001$). The incidence of infection-related death was greater in patients with DM than in patients without DM ($P < .001$; hazard ratio 3.74 [1.78-7.71]). Freedom from the recurrence of endocarditis at 1 and 5 years postoperatively was 98% and 95% in patients without DM, and 89% and 78% in patients with DM ($P < .001$), respectively. The Cox hazard analysis revealed that the presence of DM was the only independent risk for recurrence (hazard ratio 3.74 [1.45-9.54], $P = .007$).

Conclusions: The short- and mid-term outcome after valve surgery for active IE in patients with DM is worse because of the greater prevalence of infection-related death and IE recurrence. (J Thorac Cardiovasc Surg 2018;155:1021-9)

The Kaplan Meier analysis of the overall survival after valve surgery in patients with and without diabetes.

Central Message

The mid-term outcome after valve surgery for active endocarditis in patients with diabetes mellitus is worse because of the greater prevalence of infection-related death and endocarditis recurrence.

Perspective

Diabetes mellitus adversely affects infection-related death and endocarditis recurrence even after the successful discharge after valve surgery. The indication and timing of valve surgery in endocarditis should be evaluated in patients with diabetes. In addition, the prophylactic management about prevention of recurrence might be required in patients with endocarditis who have diabetes mellitus.

See Editorial Commentary page 1030.

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Despite the recent advances in the diagnosis and treatment of infective endocarditis (IE), it remains a disease with a high mortality rate.¹ Several studies have evaluated the

Scanning this QR code will take you to the supplemental figures and tables for this article.

Abbreviations and Acronyms

CVA	= cerebrovascular accident
CVVHD	= continuous veno-venous hemodialysis
DM	= diabetes mellitus
eGFR	= estimated glomerular filtration rate
IE	= infective endocarditis
LV	= left ventricular

risk factors for mortality in patients with IE^{2,3} and found that surgical intervention reduced the rate of mortality.³⁻⁵

Meanwhile, it is well known that diabetes mellitus (DM) is associated with an increased risk of infections,^{6,7} and an epidemiologic study reported that DM increased the risk of IE.⁸ In addition, several previous studies have reported that DM is associated with an increased disease severity and in-hospital mortality rate in patients with IE.^{4,9-12} However, approximately one half the patients in all these previous studies did not undergo surgical treatment. Moreover, mid-term to long-term clinical outcomes, particularly in patients with valve surgery, were not studied, and very little is known about the prognosis of patients with DM who are diagnosed with IE after valve surgery. Therefore, in the present study, we evaluated the clinical outcomes, including the short- and mid-term results, of surgical intervention for IE in patients with DM.

METHODS

Study Design

This retrospective, multicenter study was approved by the institutional review board of the Osaka University Hospital, and the use of the Osaka Cardiovascular Research Group database was approved by each affiliated hospital. Detailed records of patients who underwent valve surgery for active left-sided IE between 2009 and 2016 in 12 affiliated hospitals were obtained (Table E1). During this period, 470 patients underwent valve surgery for left-sided active IE. We compared the preoperative valuables and clinical results between patients with DM and patients without DM.

Surgery and Postoperative Treatment for Active Endocarditis

The indication and details of valve surgery were described previously.¹³ To summarize, as this was a retrospective multicenter study, the timing of valve surgery was decided by the attending surgeon at each hospital. The choice between valve repair or replacement and between mechanical valve or biological valve was at the discretion of the attending surgeon. Regarding the mitral valve endocarditis, mitral valve repair was attempted first if the infection and valve destruction were not extensive.

The postoperative antibiotics regimen was selected according to the guideline.¹⁴ Generally, intravenous antibiotics were administered for 4 weeks after the surgery, and the need for additional intravenous and/or oral antibiotic treatment was decided by each physician depending on the patient's condition.

Definitions

Left-sided active IE was defined as IE that involved the aortic valve or the mitral valve and required antibiotic therapy until the surgery. Patients with

healed IE and IE that only involved right side valve were excluded from this study. The timing of IE diagnosis was defined as the day on which the presence of vegetation was first confirmed via transthoracic or transesophageal echocardiography. In patients without obvious vegetations, the timing of diagnosis was defined as the day on which they first met modified Duke criteria for definitive endocarditis.¹⁵ As for initial intention-to-treat plan, "medical treatment first" was defined as the initial treatment with antibiotics and medication for endocarditis without any decision of definitive timing and plan for valve surgery at the timing of endocarditis diagnosis, whereas "surgery first" was defined as the initial treatment with immediate planning for urgent or emergent surgery at the timing of endocarditis diagnosis.

In the present study, the presence of DM was defined as the chronic administration of oral medication for DM and/or subcutaneous insulin use, or preoperative glycated hemoglobin level greater than 6.5%. Insulin use also was defined as requirement of chronic insulin use before the diagnosis of IE and/or since the discharge after valve surgery. Temporal intravenous and/or subcutaneous insulin infusion in the acute phase after surgery was not included into insulin use. Atrial fibrillation included both chronic and paroxysmal atrial fibrillation that was detected preoperatively. The presence of preoperative hemodialysis was defined as chronic hemodialysis for end-stage renal failure. Hypertension was defined as any preoperative episode of medical treatment for hypertension. The definition of other preoperative complications (eg, heart failure, stroke, and embolism), and postoperative complication (eg, neurologic deterioration and complete atrioventricular block) was described previously.¹³ Short- and mid-term mortality was defined as death for any reason. Cardiovascular-related death was defined as death due to a cardiovascular disease, which included stroke, heart failure, sudden death, prosthetic valve endocarditis, and acute myocardial infarction. Cerebrovascular accident (CVA)-related death was defined as any death due to a major stroke. Infection-related death was defined as death due to any infection (eg, recurrence of endocarditis, pneumonia). Endocarditis recurrence was defined as IE that required redo valve surgery for definitive prosthetic valve endocarditis or definitive endocarditis that met Duke criteria and required prolonged intravenous antibiotics therapy.

Laboratory and Echocardiographic Values

The causative organism was defined as an organism that was detected in a blood culture or a resected valve culture. If the definitive causative agents were not obtained from both blood cultures and resected valves, the causative organism was defined as unknown. Echocardiographic parameters were obtained at the time of diagnosis of IE. Vegetation size was determined based on the maximal length of the vegetation. Preoperative laboratory valuables were obtained from medical records at the time of endocarditis diagnosis and just before valve surgery. The laboratory valuables that were taken at the same day or at least 1 day before surgery was adopted for "laboratory data just before surgery." Several laboratory valuables (white blood cell counts and serum C-reactive protein, creatinine, and total bilirubin levels) also were collected postoperatively (at 1, 2, 4, and 8 weeks after the valve surgery). Estimated glomerular filtration rate (eGFR) was calculated with the following equation: $eGFR = 186 \times (\text{serum creatinine}/88.4)^{-1.154} \times (\text{age in years})^{-0.203} \times 0.742$ (if female).

Data Collection

Data collection of studied patients was mainly organized by 3 surgeons (Y.D., Y.J., and M.R.). Patient identification was performed with the Osaka Cardiovascular Research Group database, and details were collected by examining each hospital's medical records. The operative records of all patients also were reviewed, and the details of surgical procedures were collected. Follow-up investigations were performed with the information obtained from medical records or telephone contact by a physician in each hospital. In the present study, the median follow-up period was 2.2 (0.4-4.9) years. Follow-up was complete in 98% of cases as of December 31, 2016.

TABLE 1. Baseline characteristics of the overall cohort

	Diabetes mellitus (–) n = 374	Diabetes mellitus (+) n = 96	P value	Insulin (–) n = 56	Insulin (+) n = 40	P value
Baseline characteristics						
Age, y	62 (49-71)	66 (58-75)	<.001	66 (63-75)	63 (56-74)	.106
Male, n (%)	241 (64%)	64 (67%)	.720	42 (75%)	22 (55%)	.050
Body surface area, m ²	1.54 ± 0.18	1.60 ± 0.21	.092	1.60 ± 0.16	1.60 ± 0.24	.988
Body mass index, kg/m ²	20.7 (18.4-22.8)	22.3 (19.9-26.6)	.006	21.7 (20.1-24.4)	23.0 (19.7-28.5)	.382
Bacterial species						
Positive blood culture, n (%)	280 (75%)	80 (83%)	.104	47 (84%)	33 (83%)	1.000
Staphylococcus sp	103 (28%)	37 (39%)	.045	20 (36%)	17 (43%)	.530
<i>Staphylococcus aureus</i> , n (%)	71 (19%)	25 (26%)	.155	13 (23%)	12 (30%)	.487
MRSA, n (%)	24 (6%)	10 (10%)	.187	4 (7%)	6 (15%)	.311
Streptococcus species, n (%)	155 (41%)	27 (28%)	.019	17 (30%)	10 (25%)	.649
Comorbidities						
Atrial fibrillation, n (%)	46 (12%)	15 (16%)	.396	11 (20%)	4 (10%)	.260
Hemodialysis, n (%)	31 (8%)	20 (21%)	.001	5 (9%)	15 (38%)	.001
Hypertension, n (%)	83 (22%)	46 (48%)	<.001	26 (46%)	20 (50%)	.836
Antiplatelet therapy, n (%)	55 (14%)	24 (25%)	.021	14 (25%)	10 (25%)	1.000
Anticoagulation therapy, n (%)	46 (12%)	11 (11%)	1.000	8 (14%)	3 (8%)	.351
Affected valves						
Aortic valve, n (%)	177 (47%)	49 (51%)	.567	30 (54%)	19 (48%)	.679
Mitral valve involvement, n (%)	265 (71%)	64 (67%)	.454	39 (70%)	25 (63%)	.514
Double valve, n (%)	70 (19%)	17 (18%)	.820	13 (23%)	4 (10%)	.111
Prosthetic valve endocarditis, n (%)	59 (16%)	23 (24%)	.068	16 (29%)	7 (18%)	.204
Echocardiographic parameters						
LVDd, mm	54 (49-60)	50 (46-55)	.001	52 (47-57)	49 (45-54)	.052
LVDs, mm	34 (30-39)	31 (28-36)	.008	32 (30-38)	30 (27-34)	.049
Ejection fraction, %	65 (59-70)	66 (58-73)	.710	65 (58-72)	69 (56-74)	.242
Systolic tricuspid pressure gradient, mm Hg	30 (23-43)	35 (26-44)	.085	35 (25-42)	34 (28-46)	.312
Grade of the affected valve regurgitation	3.1 ± 1.1	2.7 ± 1.2	.005	2.6 ± 1.2	2.8 ± 1.1	.598
Maximum length of vegetation, mm	12 (9-16)	13 (10-19)	.032	13 (9-16)	16 (10-21)	.060
Preoperative hemodynamics						
Symptomatic heart failure, n (%)	185 (49%)	49 (51%)	.783	28 (50%)	21 (53%)	.809
Inotropic support, n (%)	91 (24%)	24 (25%)	.895	13 (23%)	11 (28%)	.634
Intubation, n (%)	44 (12%)	11 (11%)	.934	7 (13%)	4 (10%)	.705
Embolism						
Extremities, n (%)	25 (7%)	4 (4%)	.478	4 (7%)	0 (0%)	.138
Spleen, n (%)	48 (12%)	12 (13%)	.930	8 (14%)	4 (10%)	.756
Kidney, n (%)	27 (7%)	4 (4%)	.361	3 (5%)	1 (3%)	.638
Symptomatic stroke, n (%)	92 (25%)	36 (38%)	.015	25 (45%)	11 (28%)	.084
Ischemic stroke, n (%)	121 (32%)	47 (49%)	.003	28 (50%)	19 (48%)	.809
Hemorrhagic stroke, n (%)	43 (12%)	11 (11%)	.992	8 (14%)	3 (8%)	.351
Laboratory valuables at diagnosis						
White blood cell counts, ×1000/μL	10.0 (7.6-13.4)	11.8 (8.4-15.2)	.035	11.1 (8.4-13.9)	13.3 (7.8-16.1)	.135
C-reactive protein, mg/dL	6.5 (3.6-10.9)	7.8 (4.5-12.2)	.073	7.1 (5.3-12.4)	8.3 (4.2-10.9)	.945
Hemoglobin, g/dL	10.4 (9.0-11.9)	10.3 (8.7-11.4)	.405	10.7 (9.5-11.5)	9.7 (8.4-11.1)	.059
Platelet counts, ×1000/μL	188 (117-252)	168 (113-230)	.110	173 (100-228)	166 (114-232)	.331
Blood urea nitrogen, mg/dL	17 (12-28)	25 (15-42)	.003	20 (12-32)	34 (19-53)	.009
Creatinine, mg/dL	0.86 (0.70-1.20)	1.13 (0.85-2.19)	.004	0.95 (0.81-1.88)	1.57 (0.89-5.60)	.007
estimated GFR, mL/min/1.73 m ²	90 (60-114)	59 (27-92)	<.001	80 (37-95)	40 (10-67)	.010
Total bilirubin, mg/dL	0.7 (0.5-1.0)	0.7 (0.5-1.1)	.421	0.8 (0.6-1.1)	0.7 (0.4-0.9)	.467
Lactate dehydrogenase, IU/L	294 (236-412)	305 (259-383)	.849	320 (238-411)	305 (280-384)	.568
Total protein, mg/dL	6.5 (5.9-7.1)	6.3 (5.7-6.9)	.022	6.4 (5.7-6.8)	6.3 (5.2-6.9)	.261
Albumin, mg/dL	2.95 ± 0.58	2.76 ± 0.56	.014	2.79 ± 0.55	2.72 ± 0.57	.599

(Continued)

TABLE 1. Continued

	Diabetes mellitus (–) n = 374	Diabetes mellitus (+) n = 96	P value	Insulin (–) n = 56	Insulin (+) n = 40	P value
International normalization ratio	1.20 (1.11-1.36)	1.20 (1.10-1.48)	.578	1.20 (1.13-1.60)	1.15 (1.05-1.35)	.112
Duration between diagnosis and surgery, d	10 (2-26)	7 (1-21)	.230	7 (2-18)	6 (1-28)	.451
Laboratory valuables just before surgery						
White blood cell counts, $\times 1000/\mu\text{L}$	8.1 (5.8-11.3)	8.8 (6.4-12.6)	.119	9.0 (6.5-12.6)	8.7 (6.0-14.0)	.708
C-reactive protein, mg/dL	3.2 (0.8-7.2)	4.5 (1.5-10.3)	.006	5.2 (1.6-10.4)	3.7 (1.2-9.6)	.646
Hemoglobin, g/dL	10.2 (9.1-11.7)	9.9 (8.6-11.3)	.239	10.3 (9.3-11.7)	8.7 (8.2-10.9)	.017
Platelet counts, $\times 1000/\mu\text{L}$	193 (123-248)	159 (106-233)	.043	159 (102-235)	166 (115-232)	.924
Blood urea nitrogen, mg/dL	17 (12-27)	20 (14-39)	.006	17 (12-37)	28 (14-58)	.037
Creatinine, mg/dL	0.91 (0.70-1.26)	1.18 (0.82-1.97)	.001	0.98 (0.80-1.86)	1.40 (0.90-5.25)	.043
Estimated GFR, mL/min/1.73 m ²	84 (58-111)	57 (34-90)	<.001	74 (36-90)	47 (10-71)	.022
Total bilirubin, mg/dL	0.6 (0.4-0.9)	0.6 (0.4-1.0)	.541	0.7 (0.5-1.0)	0.5 (0.4-0.7)	.037
Lactate dehydrogenase, IU/L	298 (229-408)	309 (262-371)	.522	308 (260-423)	310 (269-355)	.882
International normalization ratio	1.17 (1.10-1.32)	1.20 (1.10-1.34)	.797	1.20 (1.14-1.40)	1.13 (1.05-1.26)	.031

Statistical Analysis

Statistical analysis was performed with SPSS version 23 (SAS Institute Inc, Cary, NC). Categorical variables were presented as percentages, and continuous data as means, standard deviations, or medians (interquartile range) after testing for normality using the Shapiro-Wilk W test. The comparisons between the 2 groups were performed with the χ^2 test for categorical variables, Welch *t* test, or Mann-Whitney *U* test for continuous variables, as appropriate. All *P* values for statistical analyses were 2-tailed, and *P* < .05 indicated a statistically significant difference.

Overall survival and freedom from recurrence of endocarditis rates were estimated with Kaplan-Meier curves and compared between the groups with a log-rank test. The multiple regression model was applied to identify the risk factors for in-hospital mortality after the valve surgery. Cox regression hazard models were applied to identify the risk factors for overall mortality, mortality after the first discharge, and recurrence of endocarditis. All the valuables enrolled in the analysis are listed in Table E2. To summarize, baseline characteristics, preoperative valuables, comorbidities, or complications were enrolled for risk analysis of in-hospital mortality or overall mortality rate. Similarly, baseline characteristics, preoperative and postoperative complications, and operative and postoperative valuables were enrolled for the risk analysis of mortality after the first discharge and recurrence of endocarditis. The univariate analysis initially was applied, then the factors with *P* < .05 were considered for inclusion in the multivariate multiple regression or Cox hazard model to identify the risk factors.

For further comparison of the overall survival and recurrence of endocarditis in patients with and without DM, backgrounds of 2 groups were adjusted by propensity score matching. The propensity score was obtained by multivariate logistic regression. The applied variables that have been reported as independent risk for mortality (age, heart failure, prosthetic valve endocarditis, preoperative hemodialysis, and *Staphylococcus aureus* infection) were selected in this study. We performed a 1:2 nearest-available matching algorithm with a 0.1 caliper, then 150 patients without DM and 75 patients with DM were extracted depending on the propensity score matching model.

RESULTS

During this study period, 470 patients underwent valve surgery for left-sided active IE. Of them, 96 (20%) patients had concomitant DM. We compared the preoperative valuables and clinical results between patients with DM

(*n* = 96) and patients without DM (*n* = 374). In 96 patients with DM, 40 (42%) patients required chronic subcutaneous insulin injection for DM treatment. Baseline and preoperative characteristics of the patients are summarized in Table 1. Patients with DM were significantly older and had larger body mass index than patients without DM. *Staphylococcus* species were significantly more prevalent and streptococcus species were less prevalent in patients with DM. The prevalence of chronic hemodialysis, hypertension, and antiplatelet use was significantly greater in patients with DM; particularly, chronic hemodialysis was prevalent in patients with insulin. No statistical difference in the affected valves and the proportion of prosthetic valve endocarditis was found between the groups.

Although the presence of symptomatic heart failure, requirement of inotropic support, or intubation was similar, the dimension of the left ventricle was significantly smaller in patients with DM, particularly in patients with insulin, whereas there was no statistical differences regarding the left ventricular (LV) ejection fraction among the groups. In addition, patients with DM had a trend for greater systolic tricuspid pressure gradient, although they had a lower grade of regurgitation of the affected valve. The vegetation size was significantly larger in patients with DM. Acute cerebral infarction was more prevalent in patients with DM. As for preoperative laboratory valuables (both at the time of diagnosis and just before the valve surgery), the inflammation levels were greater and the renal function was worse in patients with DM, especially in patients with insulin, whereas the liver function was similar among the 2 groups. The median duration from endocarditis diagnosis to valve surgery was 10 (2-26) days in patients without DM and 7 (1-21) days in patients with DM (*P* = .230).

The operative and postoperative outcomes of patients are detailed in Table 2. Among all patients without DM,

TABLE 2. Operative results

	Diabetes mellitus (–) n = 374	Diabetes mellitus (+) n = 96	P value	Insulin (–) n = 56	Insulin (+) n = 40	P value
Aortic valve (n = 226)	n = 177	n = 49		n = 30	n = 19	
Valve repair, n (%)	1 (1%)	0 (0%)	1.000	0 (0%)	0 (0%)	1.000
Valve replacement, n (%)	176 (99%)	49 (100%)		30 (100%)	19 (100%)	
Bioprosthetic valve, n (%)	141 (80%)	46 (94%)	.029	30 (100%)	16 (84%)	.053
Mechanical valve, n (%)	35 (20%)	3 (6%)		0 (0%)	3 (16%)	
Aortic root surgery, n (%)	17 (10%)	10 (20%)	.048	7 (23%)	3 (16%)	.720
Mitral valve (n = 329)	n = 265	n = 64		n = 39	n = 25	
Valve repair, n (%)	114 (43%)	27 (42%)	.904	17 (44%)	10 (40%)	.776
Valve replacement, n (%)	151 (57%)	37 (58%)		22 (56%)	15 (60%)	
Bioprosthetic valve, n (%)	100 (66%)	29 (78%)	.143	17 (77%)	12 (80%)	1.000
Mechanical valve, n (%)	51 (34%)	8 (22%)		5 (23%)	3 (20%)	
Requirement of CABG, n (%)	13 (3%)	12 (13%)	.002	8 (14%)	4 (10%)	.756
Requirement of double valve surgery, n (%)	68 (18%)	17 (18%)	.819	13 (23%)	4 (10%)	.111
Requirement of annular reconstruction, n (%)	61 (16%)	26 (27%)	.019	17 (30%)	9 (23%)	.390
Operative time and transfusion						
Operative time, min	311 (260-399)	335 (261-485)	.028	340 (265-578)	329 (255-407)	.043
Cardiopulmonary bypass time, min	166 (130-225)	169 (134-259)	.076	191 (138-267)	147 (122-217)	.051
Aortic clamp time, min	124 (92-167)	130 (92-199)	.046	148 (94-204)	119 (90-182)	.198
Platelet transfusion, units	0 (0-20)	10 (0-20)	.019	10 (0-30)	20 (3-20)	.704
Complications						
Requirement of ECMO, n (%)	7 (2%)	6 (6%)	.035	5 (9%)	1 (3%)	.396
Neurologic deterioration, n (%)	19 (5%)	4 (4%)	1.000	2 (4%)	2 (5%)	1.000
Mediastinitis, n (%)	4 (1%)	4 (4%)	.059	1 (2%)	3 (8%)	.305
Requirement of CVVHD, n (%)	42 (11%)	26 (27%)	<.001	16 (29%)	10 (25%)	.697
Complete AV block, n (%)	8 (2%)	2 (2%)	1.000	0 (0%)	2 (5%)	.171
Intubation duration, d	1 (0-2)	2 (1-4)	.010	2 (1-5)	2 (1-4)	.916
Duration of intravenous antibiotics, d	28 (18-37)	35 (26-42)	.005	36 (25-43)	34 (27-42)	.477
Hospital stay, d	35 (23-52)	46 (31-92)	.007	43 (27-75)	61 (32-99)	.475
30-d mortality, n (%)	16 (4%)	7 (7%)	.236	6 (11%)	1 (3%)	.234
Hospital mortality, n (%)	30 (8%)	12 (13%)	.187	8 (14%)	4 (10%)	.756
Reason of in-hospital death						
Heart failure, n (%)	9 (2%)	3 (3%)	.717	3 (5%)	0 (0%)	.263
Organ failure, n (%)	14 (4%)	6 (6%)	.300	4 (7%)	2 (5%)	1.000
Refractory infection, n (%)	9 (2%)	5 (5%)	.179	3 (5%)	2 (5%)	1.000
Cerebrovascular accident, n (%)	5 (1%)	2 (2%)	.635	1 (2%)	1 (3%)	1.000

CABG, Coronary artery bypass grafting; ECMO, extracorporeal membrane oxygenation; CVVHD, continuous veno-venous hemodialysis; AV, atrioventricular.

177 (47%) had aortic valve surgery and 265 (71%) had mitral valve surgery, including 68 (18%) patients with double valve surgery. In contrast, among patients with DM, 49 (51%) had aortic valve surgery and 64 (67%) had mitral valve surgery, including 17 (18%) with double valve surgery. No differences in the prevalence of the mitral valve repair were found between the 2 groups. In addition, a greater proportion of patients with DM required concomitant coronary artery bypass graft or annular reconstruction (patch reconstruction or aortic root surgery) for severe perivalvular abscess. Longer operative time and aortic crossclamp time was seen in patients with DM, in whom more platelet products were necessary. Postoperative

complications are also detailed in Table 2. The need for extracorporeal membranous oxygenation and continuous veno-venous hemodialysis (CVVHD) was more prevalent in patients with DM. Moreover, the duration of intubation, intravenous antibiotic therapy, and hospital stay was significantly longer in these patients. In-hospital mortality was seen in 30 (8%) patients of the non-DM group and in 12 (13%) of the DM group ($P = .187$). No differences regarding the cause of in-hospital mortality were found between the 2 groups.

We compared the change of pre- and postoperative inflammation levels and end-organ function between the DM and non-DM groups (Table E3). Although both white

FIGURE 1. The Kaplan-Meier analysis of the overall survival and its 95% confidence interval. A, Patients without DM (black line) and patients with DM (red line). B, Patients without insulin use (blue line) and patients with insulin use (orange line). C, The overall survival in 96 patients with DM according to the initial intention-to-treat plan. Patients with “surgery first” (blue line) and patients with “medical first” (orange line).

blood cell counts and serum C-reactive protein levels steadily decreased during the postoperative periods in both groups, there was a trend of greater inflammation levels in patients with DM. The renal function was significantly worse in patients with DM throughout all treatment periods; however, the renal parameters did not significantly change in time during the studied period in both groups.

The multivariate analysis of the preoperative risk factors for in-hospital mortality is shown in Table E4. The multivariate analysis revealed older age, presence of heart failure, prosthetic valve endocarditis, and lower platelet counts were independent risk factors for in-hospital mortality. The presence of diabetes was not a risk factor for in-hospital mortality.

The overall survival rate at 1, 3, and 5 years was 87%, 82%, and 81%, respectively, in the non-DM group, and 72%, 59%, and 59%, respectively, in the DM group (Figure 1, A, $P < .001$). There was no differences about overall survival between patients with and without insulin. (Figure 1, B). When we compared overall survival between

2 initial intention-to-treat plans in the DM group, there was a trend of better prognosis if patients had “surgery first” as an initial intention-to-treat plan compared with “medical treatment first” (Figure 1, C). The survival rate after the first discharge at 1, 3, and 5 years was 96%, 90%, and 88%, respectively in the non-DM group, and 84%, 68%, and 68%, respectively in the DM group (Figure E1, A, $P < .001$). Insulin use did not make an impact on survival after the first discharge (Figure E1, B). These worse survival rates in the DM group were seen especially in patients with aortic valve involvement rather than those with mitral valve involvement (Figure E2, A and B). Cox hazard analysis of the preoperative risk factors for overall mortality are summarized in Table 3. The multivariate analysis revealed that older age, DM, chronic hemodialysis, *S aureus* infection, double valve involvement, prosthetic valve endocarditis, and lower platelet counts were independent risk factors for overall mortality. In addition, the risk analysis about the baseline characteristics and operative and postoperative parameters for the overall mortality after the first discharge are shown in Table E5. The multivariate

TABLE 3. Preoperative risk factors for overall mortality

	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age, y	1.06 (1.03-1.07)	<.001	1.04 (1.02-1.07)	<.001
Diabetes mellitus	2.25 (1.45-3.42)	<.001	1.65 (1.04-2.57)	.034
Chronic hemodialysis	2.85 (1.73-4.50)	<.001	2.36 (1.17-4.70)	.017
Heart failure	1.94 (1.29-2.95)	.001	1.44 (0.93-2.29)	.106
<i>Staphylococcus aureus</i> infection	2.11 (1.35-3.23)	.002	2.09 (1.22-3.49)	.008
Double valve involvement	2.13 (1.30-3.34)	.003	1.83 (1.09-2.97)	.024
Prosthetic valve endocarditis	2.28 (1.43-3.40)	.001	2.26 (1.37-3.67)	.002
Laboratory valuables just before surgery				
Platelet counts, $\times 1000/\mu\text{L}$	0.92 (0.90-0.95)	<.001	0.95 (0.92-0.97)	.003
C-reactive protein, mg/dL	1.03 (1.00-1.05)	.031	0.99 (0.96-1.02)	.981
eGFR, mL/min/1.73 m ²	0.99 (0.98-0.99)	<.001	1.00 (0.99-1.01)	.338
Echocardiographic parameters				
LVEF, %	0.98 (0.96-1.00)	.018	0.98 (0.96-1.00)	.068

CI, Confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricle ejection fraction.

FIGURE 2. The Kaplan-Meier analysis of the free from A, cardiovascular-related death; B, cerebrovascular accident-related death; and C, infection-related death.

analysis revealed that older age, presence of DM, greater C-reactive protein level at 2 weeks after surgery, and low ejection fraction were independent risk factors for overall mortality after the first discharge. Because the presence of chronic hemodialysis, *S aureus* endocarditis, and prosthetic valve endocarditis were the independent risk factors for overall mortality as well as DM, we further analyzed the overall mortality according to the stratification about presence of DM and these parameters (Figure E3, A-C). When we analyzed overall mortality in the propensity matched cohort, the overall survival was still significantly worse in patients with DM ($P = .008$, Figure E4, A).

We further subdivided the cause of death into several reasons and compared them between the 2 groups. The rates of free from cardiovascular-related death, CVA-related death, and infection-related death are shown in Figure 2, A and C. Although there was no statistical difference about cardiovascular-related death and CVA-related death between the 2 groups, the free from infection-related death was significantly lower in patients with DM ($P < .001$, hazard ratio 3.74 [1.78-7.71]).

During the follow-up period, 21 patients developed recurrence of endocarditis. The rate of freedom from recurrence of endocarditis at 1, 3, and 5 years was 98%, 97%, and 95%, respectively in the non-DM group and

89%, 83%, and 78%, respectively, in the DM group (Figure 3, A, $P < .001$). There were no statistical differences about recurrence of endocarditis between patients with and without insulin use (Figure 3, B). The Cox hazard risk analysis of the baseline, operative, and postoperative risk factors for recurrence of endocarditis are shown in Table 4. Univariate analysis showed that the presence of DM, prosthetic valve endocarditis, perivalvular abscess, and requirement of postoperative CVVHD were risk factors for the recurrence of endocarditis. Multivariate risk analysis revealed that the presence of DM was the only independent risk factor for the recurrence of endocarditis (hazard ratio 3.74 [1.45-9.54], $P = .007$). When we analyzed in the propensity matched cohort, the rate of freedom from recurrence of endocarditis was also significantly worse in patients with DM ($P = .004$, Figure E4, B).

DISCUSSION

In the present study, patients with DM had a more severe preoperative condition than patients without DM. *Staphylococcus* species, which has been reported as a risk factor for mortality,^{4,5} was more common in patients with DM. There have been controversies about relationship between DM and heart failure in patients with IE.^{10,12,16} In the present study, although the presence

FIGURE 3. The Kaplan-Meier analysis of the rate of freedom from recurrence of endocarditis. A, Patients without DM (black line) and patients with DM (red line). B, Patients without insulin use (blue line) and patients with insulin use (orange line).

TABLE 4. Risk factors for recurrence of endocarditis

	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Diabetes mellitus	4.50 (1.78-11.2)	.002	3.74 (1.45-9.54)	.007
Prosthetic valve endocarditis	2.89 (1.08-7.21)	.036	2.06 (0.64-6.23)	.219
Perivalvular abscess	3.03 (1.13-7.53)	.030	2.04 (0.65-5.98)	.215
Need of postoperative CVVHD	4.68 (1.48-12.6)	.011	3.12 (0.96-8.81)	.059

CI, Confidence interval; CVVHD, continuous veno-venous hemodialysis.

of symptomatic heart failure and the LV ejection fraction were similar between the groups and the degree of regurgitation of the affected valve was lower in patients with DM, they had smaller LV dimensions and greater systolic tricuspid pressure gradients. These results could be interpreted by the LV diastolic dysfunction in patients with DM.¹⁷ Furthermore, in the present study, 20% of patients with DM received chronic hemodialysis, and median eGFR was significantly lower in patients with DM. Renal dysfunction has been reported to be one of the risk factors for mortality in patients with IE.^{5,10,18} It is reasonable that some severe preoperative conditions predispose patients with DM to several postoperative complications (eg, mediastinitis or the requirement of CVVHD or extracorporeal membranous oxygenation) and longer intravenous antibiotic therapy and hospital stay even, although there was no statistical significance for in-hospital mortality.

Several reports evaluated the negative impact of DM on in-hospital mortality or short-term mortality, although these previous reports were composed of many patients who did not undergo valve surgery in the acute phase of IE.^{1,3,4,10,16} Furthermore, importantly, patients with DM were more likely to avoid valve surgery because of the poorer health condition at IE diagnosis.² Therefore, studies that analyzed the impact of DM on mortality rates after valve surgery are very limited. Gaca and colleagues¹⁹ reported in a study based on the Society of Thoracic Surgeons database that DM (both insulin dependent and insulin independent) was one of the predictors of 30-day mortality after valve surgery for IE, although the clinical results after the discharge was unknown. Our study first evaluated that patients with DM had worse survival rate even after once they survived valve surgery, because the infection related-death was more prevalent in them even though the prevalence of CVA- or cardiovascular-related death was similar between patients with DM and without DM. This similarity of cardiovascular-related and CVA-related mortality in patients with DM was probably because cardiac function was relatively preserved with their median ejection fraction of 66%, and the cause of CVA in IE patients (eg, rupture of mycotic aneurysm, embolism of vegetation) is fundamentally different from CVA in

general DM population.^{20,21} To the best of our knowledge, we revealed for the first time that DM does not affect cardiovascular-related or CVA-related mortality in short- and mid-term follow-up period.

The recurrence of IE is one of the main concerns in patients who undergo valve surgery for active IE. Although the greater infection-related mortality rates in patients with DM may be related to the adverse effects of hyperglycemia on immune function in general population,^{22,23} a limited number of studies investigated the impact of DM on IE recurrence. Several previous studies have evaluated that the freedom from IE recurrence after valve surgery was between 80% and 90% at 5 years, although the predictors of IE recurrence were not analyzed.^{18,24,25} Renzulli and colleagues²⁶ reported that not DM, but prosthetic valve endocarditis, positive valve culture, and persistent fever at seventh postoperative day were the predictors of IE recurrence. In the present study, the presence of DM was the only independent predictor of IE recurrence, and approximately 10% of patients with DM developed IE recurrence during the first year. Although no guidelines and studies about the efficacy of life-long prophylactic therapy for prevention of recurrence after valve surgery for IE are available, oral prophylactic antibiotics therapy after the discharge might be considered in patients with DM.

The present study has several limitations. First, the present study was a retrospective multicenter study with a limited number of patients in each hospital. Although the basic strategy was managed according to the guideline, it is possible that there was a difference in treatment strategy (eg, timing of surgery, antibiotics duration). Second, though the analysis about the impact of insulin dependence on mortality in patients with IE was evaluated, the total number of patients with insulin was limited; therefore, further evaluation about the impact of insulin is demanded. In addition, the impact of diabetes control on outcome could not be evaluated. Third, the data about the oral antibiotic therapy after the discharge could not be collected. Finally, we only collected data about the incidence of death and its cause, and we could not collect data about each adverse event after the first discharge. As for IE recurrence, there was possible that different bacterial species accidentally

caused de novo endocarditis after valve surgery, although majority of IE recurrence patients had the same species with the previous IE.

In conclusion, patients with DM who have active IE have a more severe condition before valve surgery than patients without DM. The short- and mid-term prognosis is poor in patients with DM who have IE because of the relatively greater prevalence of infection-related death and the relatively greater rate of IE recurrence.

Conflicts of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: endocarditis, diabetes mellitus, valve surgery

FIGURE E1. The Kaplan-Meier analysis of the overall survival after the first discharge and its 95% confidence interval. A, Patients without DM (black line) and patients with DM (red line). B, Patients without insulin use (blue line) and patients with insulin use (orange line).

FIGURE E2. The Kaplan-Meier analysis of the overall survival and its 95% confidence interval between patients without DM (black line) and patients with DM (red line) in A, aortic valve endocarditis and B, mitral valve endocarditis. (Double valve endocarditis patients were excluded.)

FIGURE E3. The Kaplan-Meier analysis of the overall survival rate according to the presence of diabetes mellitus and (A) *Staphylococcus aureus* infection; B, chronic hemodialysis; and (C) prosthetic valve endocarditis. DM, Diabetes mellitus; HD, chronic hemodialysis; PVE, prosthetic valve endocarditis.

FIGURE E4. A, The Kaplan-Meier analysis of the overall survival and its 95% confidence interval between patients with and without DM in the propensity matched cohort. B, The Kaplan-Meier analysis of the rate of freedom from recurrence of endocarditis in the propensity matched cohort. Patients without DM (black line) and patients with DM (red line).

TABLE E1. List of participating hospitals in this multicenter study

Osaka University Hospital (Osaka, Japan)
Dokkyo Medical University Hospital (Tochigi, Japan)
Osaka Police Hospital (Osaka, Japan)
Osaka National Hospital (Osaka, Japan)
Osaka Prefectural General Hospital (Osaka, Japan)
JCHO Osaka Hospital (Osaka, Japan)
Fukui Cardiovascular Hospital (Fukui, Japan)
Higashi-Takarazuka Satoh Hospital (Hyogo, Japan)
Rinku General Hospital (Osaka, Japan)
Kansai Rosai Hospital (Hyogo, Japan)
Kinan Hospital (Wakayama, Japan)
Heart Institute Sakakibara Hospital (Okayama, Japan)

TABLE E2. Variables enrolled in the univariate and multivariable analysis for risk factors

Multiple regression model		Cox hazard model	
In-hospital mortality	Overall mortality	Mortality after the first discharge	Recurrence of endocarditis
Age	Age	Age	Age
Male	Male	Male	Male
Body surface area	Body surface area	Body surface area	Body surface area
Body mass index	Body mass index	Body mass index	Body mass index
Atrial fibrillation	Atrial fibrillation	Atrial fibrillation	
Diabetes mellitus	Diabetes mellitus	Diabetes mellitus	Diabetes mellitus
Chronic hemodialysis	Chronic hemodialysis	Chronic hemodialysis	Chronic hemodialysis
Preoperative stroke	Preoperative stroke	Preoperative stroke	
Preoperative heart failure	Preoperative heart failure	Preoperative heart failure	
			MRSA
<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>
Double valve involvement	Double valve involvement	Double valve replacement	Double valve replacement
Prosthetic valve endocarditis	Prosthetic valve endocarditis	Prosthetic valve endocarditis	Prosthetic valve endocarditis
			Use of mechanical valve
Laboratory valuables just before surgery	Laboratory valuables just before surgery		Reconstruction of annulus
White blood cell counts ($\times 1000/\mu\text{L}$)	White blood cell counts ($\times 1000/\mu\text{L}$)	Perioperative stroke	Perioperative stroke
Hemoglobin (g/dL)	Hemoglobin (g/dL)	Mediastinitis	Mediastinitis
Platelets ($\times 10,000/\mu\text{L}$)	Platelets ($\times 10,000/\mu\text{L}$)	Need of CVVHD	Need of CVVHD
C-reactive protein (mg/dL)	C-reactive protein (mg/dL)		
Total bilirubin (mg/dL)	Total bilirubin (mg/dL)	Laboratory data 2 wk after surgery	Laboratory data 2 wk after surgery
eGFR (mL/min/1.73 m ²)	eGFR (mL/min/1.73 m ²)	White blood cell counts ($\times 1000/\mu\text{L}$)	White blood cell counts ($\times 1000/\mu\text{L}$)
		C-reactive protein (mg/dL)	C-reactive protein (mg/dL)
Preoperative echocardiography	Preoperative echocardiography	Total bilirubin (mg/dL)	Total bilirubin (mg/dL)
LVDd (mm)	LVDd (mm)	eGFR (mL/min/1.73 m ²)	eGFR (mL/min/1.73 m ²)
LVDs (mm)	LVDs (mm)		
LVEF (%)	LVEF (%)	Postoperative echocardiography	Duration of postoperative ABx (d)
		LVDd (mm)	
		LVDs (mm)	Postoperative echocardiography
		LVEF (%)	LVDd (mm)
			LVDs (mm)
			LVEF (%)

MRSA, Methicillin-resistant *Staphylococcus aureus*; CVVHD, continuous veno-venous hemodialysis; eGFR, estimated glomerular filtration rate; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; ABx, intravenous antibiotics therapy.

TABLE E3. Change in laboratory data before and after surgery

	Preoperative		Postoperative			
	At the time of diagnosis (95% CI)	Before operation (95% CI)	1 week (95% CI)	2 weeks (95% CI)	4 weeks (95% CI)	8 weeks (95% CI)
White blood cell counts, × 1000/ μ L						
Diabetes mellitus (–)	10.0 (7.6-13.3)	8.1 (5.8-11.3)	8.0 (6.0-10.4)	7.0 (5.4-8.7)	5.7 (4.2-7.5)	5.7 (5.0-7.3)
Diabetes mellitus (+)	12.0 (8.0-15.3)*	8.8 (6.4-12.6)	9.0 (6.8-11.6)	8.3 (6.0-10.3)*	6.3 (4.9-8.1)	6.9 (5.6-7.9)
C-reactive protein, mg/dL						
Diabetes mellitus (–)	6.4 (3.4-11.0)	3.2 (0.8-7.2)	4.8 (2.9-7.7)	2.6 (1.1-4.4)	0.7 (0.2-2.1)	0.2 (0.1-0.7)
Diabetes mellitus (+)	7.9 (4.5-12.5)	4.5 (1.5-10.3)*	5.5 (3.8-9.0)	3.0 (1.4-6.8)	1.0 (0.4-3.4)	0.5 (0.2-1.6)*
eGFR, mL/min/1.73 m ²						
Diabetes mellitus (–)	89 (59-112)	84 (58-111)	89 (63-120)	87 (55-112)	85 (51-108)	80 (57-108)
Diabetes mellitus (+)	60 (32-91)*	57 (34-90)*	64 (32-90)*	65 (35-92)*	67 (30-92)*	69 (31-88)*
Total bilirubin, mg/dL						
Diabetes mellitus (–)	0.7 (0.5-1.0)	0.6 (0.4-0.9)	0.7 (0.5-1.2)	0.6 (0.4-0.9)	0.5 (0.4-0.8)	0.5 (0.4-0.6)
Diabetes mellitus (+)	0.7 (0.5-1.1)	0.6 (0.4-1.0)	0.9 (0.6-2.6)	0.8 (0.4-1.4)	0.6 (0.4-0.7)	0.6 (0.4-0.9)
Lactate dehydrogenase, U/L						
Diabetes mellitus (–)	289 (236-412)	298 (229-408)	338 (277-437)	344 (252-415)	274 (223-357)	257 (207-319)
Diabetes mellitus (+)	310 (249-373)	309 (262-371)	349 (315-406)	305 (243-375)	266 (209-357)	258 (213-278)

CI, Confidence interval; eGFR, estimated glomerular filtration rate. * $P < .05$ compared with diabetes mellitus (–).

TABLE E4. Preoperative risk factors for in-hospital mortality

	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, y	1.06 (1.03-1.09)	<.001	1.03 (1.00-1.07)	.025
Chronic hemodialysis	3.03 (1.32-6.47)	.010	1.56 (0.49-4.82)	.440
Diabetes mellitus	1.71 (0.81-3.42)	.143		
Heart failure	4.23 (2.05-9.62)	<.001	3.47 (1.45-9.34)	.005
<i>Staphylococcus aureus</i> infection	3.68 (1.87-7.17)	<.001	3.35 (1.43-7.89)	.006
Prosthetic valve endocarditis	2.66 (1.30-5.28)	.009	3.10 (1.30-7.40)	.012
Platelet counts, × 10,000/ μ L	0.86 (0.81-0.90)	<.001	0.89 (0.81-0.90)	<.001
eGFR, mL/min/1.73 m ²	0.99 (0.98-1.00)	.009	1.00 (0.99-1.01)	.669

CI, Confidence interval; eGFR, estimated glomerular filtration rate.

TABLE E5. Risk factors for mortality after the first discharge

	Univariate		Multivariate	
	Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
Age, y	1.05 (1.03-1.07)	<.001	1.07 (1.03-1.10)	<.001
Diabetes mellitus	2.80 (1.57-4.83)	.001	2.02 (1.02-3.83)	.043
Chronic hemodialysis	2.86 (1.44-5.27)	.004	2.26 (0.78-6.41)	.133
Double valve replacement	1.98 (1.11-3.28)	.021	1.53 (0.64-3.23)	.319
Laboratory valuables 2 wk after surgery				
C-reactive protein, mg/dL	1.11 (1.06-1.15)	<.001	1.10 (1.04-1.15)	.001
eGFR, mL/min/1.73 m ²	0.99 (0.98-0.99)	<.001	1.00 (0.99-1.01)	.377
Postoperative echocardiographic parameters				
LVEF, %	0.97 (0.95-0.99)	.030	0.96 (0.94-0.99)	.003

CI, Confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricle ejection fraction.