Nationwide cohort study of mitral valve repair versus replacement for infective endocarditis

Check for updates

Hsiu-An Lee, MD,[a] Yu-Ting Cheng, MD,[a] Victor Chien-Chia Wu, MD,[b] An-Hsun Chou, MD, PhD,[c] Pao-Hsien Chu, MD,[b] Feng-Chun Tsai, MD,[a] and Shao-Wei Chen, MD[a,d]

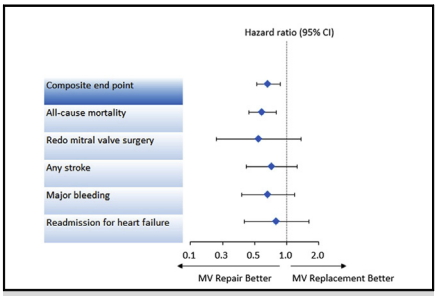
ABSTRACT

Objectives: The feasibility and long-term outcomes of mitral valve (MV) repair in patients with infective endocarditis (IE) remain unclear.

Methods: Using Taiwan's National Health Insurance Research Database, we identified 1999 patients who underwent MV surgery for IE during 2000 to 2013. The patients were more likely to have undergone valve replacement (1575 patients; 78.8%) than valve repair (424 patients; 21.2%). After 1:1 propensity score matching, 352 patients in each group were included for analysis. Perioperative outcomes and late composite end points, comprising all-cause mortality, MV reoperation, any stroke, major bleeding, and readmission for heart failure, were compared.

Results: Patients who received MV repair had fewer perioperative complications, lower in-hospital mortality rates (6.3% vs 10.8%; $P = .031$), and lower risks of late mortality (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.44-0.80), and composite end point (HR, 0.67; 95% CI, 0.52-0.87) during a mean follow-up of 4.8 years. Subgroup analysis revealed a trend in which the beneficial effect of MV repair was not apparent when surgeries were performed in hospitals within the lowest volume quartile (P for interaction $= .091$). In patients who underwent surgery during active IE, MV repair was also related to a lower rate of late mortality (HR, 0.64; 95% CI, 0.48-0.85).

Conclusions: Mitral repair for IE has better perioperative and late outcomes than mitral replacement. Mitral repair performed by an experienced team is recommended for IE patients instead of MV replacement whenever possible, even with an active infection status. (J Thorac Cardiovasc Surg 2018;156:1473-83)



Mitral valve repair results in lower rates of late mortality and composite end point.

Central Message

Mitral repair for infective endocarditis has better perioperative and late outcomes than mitral replacement, and is recommended whenever possible, even for patients with an active infection status.

Perspective

The feasibility and long-term outcomes of mitral repair for infective endocarditis remain unclear. This nationwide population-based propensity score-matching study showed better perioperative and late outcomes after mitral repair than valve replacement, even in patients with active endocarditis. In low-volume centers, the repair rate was significantly lower and the beneficial effect of repair was less apparent.

See Editorial Commentary page 1484.

See Editorial page 1471.

The incidence of infective endocarditis (IE)-related hospitalization in Taiwan is approximately 6.43 episodes per 100,000 people annually.[1] Despite improvements in diagnosis and management, in-hospital mortality of IE

Scanning this QR code will take you to the supplemental tables, figure, and video for this article.

From the [a]Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Departments of [b]Cardiology, and [c]Anesthesiology, Chang Gung Memorial Hospital, Linkou Medical Center, and [d]Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan City, Taiwan.

Received for publication Dec 4, 2017; revisions received March 28, 2018; accepted for publication April 12, 2018; available ahead of print May 26, 2018.

Address for reprints: Shao-Wei Chen, MD, Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, No 5 Fuxing St, Gueishan District, Taoyuan City 33305, Taiwan (E-mail: josephchen0314@gmail.com).

0022-5223

Copyright © 2018 by The American Association for Thoracic Surgery. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jtcvs.2018.04.064

Abbreviations and Acronyms

ASMD = absolute standardized mean difference
CI = confidence interval
HR = hazard ratio
ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification
IE = infective endocarditis
MV = mitral valve
NHI = National Health Insurance
NHIRD = National Health Insurance Research Database

remains between 20% and 30%.[2,3] Although many patients are treated successfully with antibiotics, numerous patients still require surgery because of persistent sepsis, severe valvular destruction with heart failure, or repeated embolic complications.

If mitral valve (MV) surgery is indicated, valve repair is recommended over valve replacement whenever possible.[4] The feasibility and durability of repair in degenerative mitral regurgitation caused by leaflet prolapse or chordal rupture have been well established,[5-8] but the reparability and long-term outcomes of repair in IE remain questionable. Several studies have reported improved outcome after MV repair compared with MV replacement,[8-11] but others have not reported significant differences.[12,13] However, these were all retrospective studies with an inherent selection bias. Furthermore, long-term follow-up was limited. Therefore, we conducted this study to evaluate the perioperative and late outcomes of MV repair and replacement in patients with IE by using a nationwide population-based cohort study design with propensity score matched analysis to minimize confounding factors.

METHODS

Data Source

Taiwan's National Health Insurance (NHI) program is a universal compulsory health insurance system providing comprehensive medical care coverage to 99% of the country's 23.74 million people. Derived from the NHI program, the National Health Insurance Research Database (NHIRD) contains data that accurately represent Taiwan's population, with only minimal omitted data and a small participation bias.

The NHI program has a consistent data encryption process, allowing continuous tracking of all claims of each individual within the program. Moreover, because of the mandatory enrollment and affordability of the NHI program, even people who emigrate to other countries retain their NHI identities and return to Taiwan for medical treatment, especially those who have undergone major surgeries. Thus, nearly complete long-term follow-up of all patients is possible.

All data in the NHIRD are deidentified and anonymized to protect privacy; thus, this study was exempt from a full review by the Ethics Institutional Review Board of Chang Gung Memorial Hospital. Other relevant details have been described in previous publications.[14-16]

Study Population

A total of 15,111 patients who received MV surgery between January 1, 2000 and December 31, 2013 were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes (35.12, 35.23, and 35.24) and Taiwan NHI procedure codes (68015, 68016, 68017, and 68018), which are used for reimbursement claims (Figure 1). Of these patients, 2025 (13.4%) had a history of IE or a principal diagnosis of IE during the index hospitalization. ICD-9-CM diagnosis codes (421.0, 421.1, and 421.9) were used to identify the diagnosis of IE. Patients were excluded if they were aged younger than 18 years or had received previous valve surgery.

During the study period, 1999 adult patients underwent first-time MV surgery because of IE. Types of MV surgery were distinguished using ICD-9-CM procedure codes (35.12 for MV repair; 35.23 and 35.24 for MV replacement). Patients were more likely to undergo valve replacement (1575 patients; 78.8%) than repair (424 patients; 21.2%) in our study population. Longitudinal data for MV repair and replacement revealed an increase in the proportion of valve repair from 2000 to 2013 (P for trend = .047; Figure 1, *B*). To minimize potential selection bias, we calculated a propensity score from selected variables (Table 1) and matched each patient in the MV repair group with each patient in the MV replacement group. Finally, 352 patients from each group were identified and were eligible for analysis (Figure 1, *A*).

Baseline Characteristics and Outcomes

The examined demographic characteristics are listed in Table 1. Active IE was defined as a new diagnosis of IE during the index hospitalization (Table E3). Hospital level and the hospital's total volume of valve surgery and MV repair within the study period were also examined according to NHIRD claims data. Other surgical details were identified using Taiwan NHI procedure codes.

The examined outcomes during the index hospitalization are listed in Table 2. The primary outcome during follow-up was a composite of all-cause mortality, redo MV surgery, any stroke, major bleeding, and readmission for heart failure.

Death records and records of withdrawal from the NHI program were used to identify mortality. This method has been validated in previous studies.[17,18] The date on which a patient was admitted for MV surgery was defined as the index hospitalization. The patients were followed from their index hospitalization to December 31, 2013 or date of death, with a >99% completeness of follow-up.

Statistical Analysis

Before comparing outcomes between the MV repair and MV replacement groups, we performed propensity score matching to minimize the selection bias caused by an imbalanced distribution of baseline characteristics. The propensity score was calculated on the basis of clinical and surgical characteristics (Table 1 lists all variables, except for follow-up years), including date of the index hospitalization, which might be related to the probability of receiving MV repair. Although the number of patients was considerably greater in the MV replacement group, we adopted a 1:1 matching ratio to ensure higher precision and lower bias of treatment effects.[19] Greedy nearest neighbor matching was performed in which the caliper width was set as 0.2 of the SD of the logit of the propensity score.[20] An absolute standardized mean difference (ASMD) of <0.1 after propensity score matching was considered to indicate an adequate balance of the distribution of covariates.[21]

Data regarding clinical and surgical characteristics are presented as frequency and proportion for categorical variables or as mean ± SD for continuous variables. We compared the perioperative and in-hospital outcomes between the MV repair and MV replacement groups using a McNemar test for categorical parameters (eg, in-hospital mortality) or a paired sample t test for continuous parameters (eg, volume of transfusion).

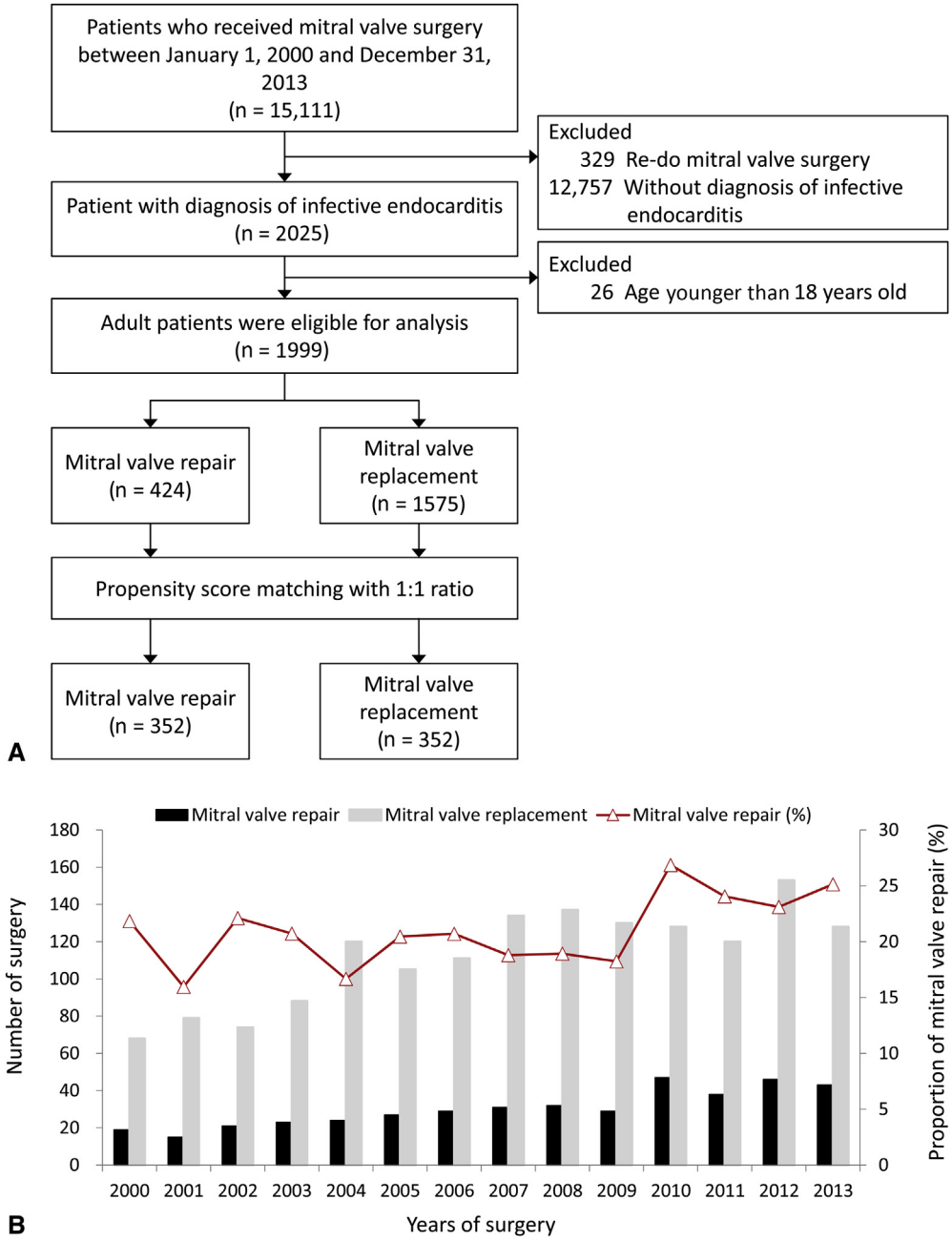


FIGURE 1. A, Flow chart of patient inclusion and exclusion criteria, and (B) bar chart illustrating the increase in the proportion of mitral valve repair from 2000 to 2013.

The risks of outcomes related to death (ie, all-cause mortality and composite end point) were compared between the study groups using a Cox proportional hazards model. In addition, we compared the risks of other late outcomes (eg, redo MV surgery, any stroke, major bleeding, and readmission for heart failure) between the study groups using a subdistribution hazards model, in which death was considered a competing risk.[22] The Cox model as well as the subdistribution hazards model were stratified according to the matched pairs. For time to event outcomes, we performed a sensitivity analysis using doubly robust adjustment.[23] The survival curves were plotted using Kaplan–Meier estimates along with a log rank test to compare group differences before propensity score matching. Finally, the proportion of microbiology between the study groups was compared using a McNemar test. Data analysis and propensity score matching were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Characteristics

Before propensity score matching, patients in the MV repair group were younger, had a lower prevalence of active IE, had a lower proportion of urgent or emergent surgery, and had a lower prevalence of comorbidities including

TABLE 1. Clinical and surgical characteristics of the study population before and after propensity score matching

Variable	Before matching				After matching		
	Total (N = 1999)	Mitral valve repair (n = 424)	Mitral valve replacement (n = 1575)	ASMD	Mitral valve repair (n = 352)	Mitral valve replacement (n = 352)	ASMD
Age, y	51.8 ± 15.9	49.3 ± 16.1	52.4 ± 15.8	0.197	50.1 ± 15.7	50.7 ± 16.1	0.035
Age group							
<40 y	499 (25.0)	131 (30.9)	368 (23.4)	0.170	98 (27.8)	96 (27.3)	0.013
40-59 y	842 (42.1)	173 (40.8)	669 (42.5)	0.034	151 (42.9)	148 (42.0)	0.017
≥60 y	658 (32.9)	120 (28.3)	538 (34.2)	0.127	103 (29.3)	108 (30.7)	0.031
Male gender	1337 (66.9)	293 (69.1)	1044 (66.3)	0.060	247 (70.2)	246 (69.9)	0.006
Active IE	1539 (77.0)	287 (67.7)	1252 (79.5)	0.270	251 (71.3)	260 (73.9)	0.057
Urgent or emergent surgery	266 (13.3)	37 (8.7)	229 (14.5)	0.182	35 (9.9)	29 (8.2)	0.059
Previous valve disease etiology							
Rheumatic heart history	295 (14.8)	52 (12.3)	243 (15.4)	0.092	50 (14.2)	54 (15.3)	0.032
Congenital heart disease	25 (1.3)	8 (1.9)	17 (1.1)	0.067	7 (2.0)	4 (1.1)	0.069
Comorbid conditions							
Old stroke	277 (13.9)	63 (14.9)	214 (13.6)	0.036	49 (13.9)	54 (15.3)	0.040
Diabetes mellitus	355 (17.8)	53 (12.5)	302 (19.2)	0.184	48 (13.6)	42 (11.9)	0.051
Hypertension	611 (30.6)	117 (27.6)	494 (31.4)	0.083	98 (27.8)	103 (29.3)	0.031
Heart failure	526 (26.3)	119 (28.1)	407 (25.8)	0.050	99 (28.1)	100 (28.4)	0.006
Coronary arterial disease	406 (20.3)	69 (16.3)	337 (21.4)	0.131	60 (17.0)	59 (16.8)	0.008
Atrial fibrillation	378 (18.9)	82 (19.3)	296 (18.8)	0.014	71 (20.2)	68 (19.3)	0.021
Dialysis	109 (5.5)	13 (3.1)	96 (6.1)	0.145	11 (3.1)	14 (4.0)	0.046
Chronic obstructive pulmonary disease	98 (4.9)	15 (3.5)	83 (5.3)	0.084	14 (4.0)	15 (4.3)	0.014
Liver cirrhosis	98 (4.9)	22 (5.2)	76 (4.8)	0.017	18 (5.1)	18 (5.1)	0.000
Gastrointestinal bleeding history	340 (17.0)	61 (14.4)	279 (17.7)	0.091	55 (15.6)	53 (15.1)	0.016
Drug abuse	45 (2.3)	8 (1.9)	37 (2.3)	0.032	7 (2.0)	3 (0.9)	0.096
Charlson total score	2.0 ± 2.1	1.7 ± 1.8	2.1 ± 2.1	0.222	1.7 ± 1.9	1.8 ± 2.0	0.065
Hospital level							
Medical center (teaching hospital)	1504 (75.2)	390 (92.0)	1114 (70.7)	0.567	318 (90.3)	314 (89.2)	0.038
Regional/district hospital	495 (24.8)	34 (8.0)	461 (29.3)	0.567	34 (9.7)	38 (10.8)	0.038
Center volume of valve surgery between 2000 and 2013							
First quartile (2-515)	503 (25.2)	41 (9.7)	462 (29.3)	0.512	40 (11.4)	27 (7.7)	0.126
Second quartile (614-1519)	507 (25.4)	82 (19.3)	425 (27.0)	0.182	72 (20.5)	76 (21.6)	0.028
Third quartile (2045-2809)	439 (22.0)	95 (22.4)	344 (21.8)	0.014	81 (23.0)	84 (23.9)	0.020
Fourth quartile (3119-4037)	550 (27.5)	206 (48.6)	344 (21.8)	0.583	159 (45.2)	165 (46.9)	0.034
Center volume of MV repair surgery between 2000 and 2013							
First quartile (0-39)	496 (24.8)	17 (4.0)	479 (30.4)	0.747	17 (4.8)	15 (4.3)	0.027
Second quartile (44-89)	481 (24.1)	57 (13.4)	424 (26.9)	0.341	56 (15.9)	49 (13.9)	0.056
Third quartile (100-451)	517 (25.9)	121 (28.5)	396 (25.1)	0.077	111 (31.5)	114 (32.4)	0.018
Fourth quartile (585-858)	505 (25.3)	229 (54.0)	276 (17.5)	0.823	168 (47.7)	174 (49.4)	0.034
Additional valve surgery							
Aortic valve replacement with mechanical prosthesis	206 (10.3)	45 (10.6)	161 (10.2)	0.013	38 (10.8)	39 (11.1)	0.009
Aortic valve replacement with bioprosthesis	115 (5.8)	52 (12.3)	63 (4.0)	0.306	28 (8.0)	31 (8.8)	0.031

(Continued)

TABLE 1. Continued

Variable	Before matching				After matching		
	Total (N = 1999)	Mitral valve repair (n = 424)	Mitral valve replacement (n = 1575)	ASMD	Mitral valve repair (n = 352)	Mitral valve replacement (n = 352)	ASMD
Tricuspid valve repair or replacement	228 (11.4)	56 (13.2)	172 (10.9)	0.070	48 (13.6)	46 (13.1)	0.017
Additional surgery							
Coronary arterial bypass surgery	130 (6.5)	26 (6.1)	104 (6.6)	0.019	23 (6.5)	22 (6.3)	0.012
Aortic surgery	24 (1.2)	9 (2.1)	15 (1.0)	0.095	4 (1.1)	3 (0.9)	0.029
Congenital heart disease correction	22 (1.1)	7 (1.7)	15 (1.0)	0.062	6 (1.7)	4 (1.1)	0.048
Follow-up year	4.5 ± 3.9	4.9 ± 4.0	4.4 ± 3.9	0.124	5.0 ± 4.0	4.6 ± 4.0	0.098

ASMD, Absolute standardized mean difference; *IE*, infective endocarditis; *MV*, mitral valve.

diabetes mellitus, coronary arterial disease, and end-stage renal disease (ASMD > 0.1). Considering hospital level and experience, medical centers and hospitals with higher volumes of valve surgery or MV repair were more likely to perform MV repair, whereas regional and district hospitals as well as those with less experience had higher proportions of MV replacement. After propensity score matching, all baseline characteristics and concomitant procedures were similar between the MV repair and replacement groups (ASMD < 0.1). Differences in hospital level and volumes were also minimized (Table 1).

In-Hospital Outcomes

Table 2 shows the in-hospital outcomes of MV repair versus MV replacement. In the propensity score-matched samples, the risks of new-onset stroke (6.5% vs 11.4%; $P = .036$), new-onset ischemic stroke (3.7% vs 8.5%; $P = .014$), massive blood transfusion (11.4% vs 20.2%; $P = .002$), and in-hospital mortality (6.3% vs 10.8%; $P = .037$) were significantly lower in patients who received MV repair than in those who received MV replacement. Compared with those who received MV replacement, patients who received MV repair had shorter intensive care unit duration of stay, shorter hospital stays, and lower in-hospital expenditures.

Late Outcomes

During a mean follow-up of 4.8 years (SD, 4 years), the rates of the composite end point were 29.3% and 41.2% in the MV repair and MV replacement groups, respectively (Table E2). This result indicates a beneficial effect in the MV repair group versus the MV replacement group (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.46–0.850.8; $P = .003$). The proportions of mortality were 19.3% and 31% in the MV repair and MV replacement groups, respectively. A similar result was observed when comparing group differences, with patients in the MV repair group having a significantly lower late mortality risk than those in the MV replacement group (HR, 0.52; 95% CI, 0.37-0.75; $P < .001$). However, no statistical difference existed regarding MV reoperation, stroke, major bleeding, or readmissions caused by heart failure (Figure 2, *A*, Table E1). Figure 2, *B* illustrates the Kaplan–Meier event-free survival (free from composite end point) curves derived for the 2 groups.

Subgroup Analysis

To evaluate which patients would benefit from MV repair the most (or least), we divided them into subgroups according to the following characteristics: age, gender, whether valve surgery was performed during active IE, urgent or emergent surgery, previous stroke, gastrointestinal bleeding, rheumatic heart disease, concomitant procedure, concomitant valve surgery, concomitant aortic valve replacement with mechanical prosthesis, and hospital volume of valve surgery and MV repair surgery (Figure 3). The beneficial effects of MV repair on the composite end point during follow-up were comparable across various levels of the selected patient characteristics (P for interaction, >.05). A trend was noted in which the beneficial effect of MV repair was less apparent in patients who received surgery in hospitals with a lower volume of MV repair; however, this was nonsignificant (P for interaction, .091).

Patients Who Underwent Valve Surgery During Active IE and Their Microbiology

We analyzed patients who underwent valve surgery during active IE before propensity score matching (Table E3). The results revealed that patients who underwent MV repair had lower all-cause mortality during follow-up (P for log-rank test, <.001; Figure 4). When comparing microbiology, we discovered that patients with active staphylococcal infections seemed to have a lower opportunity for MV repair, whereas patients with

TABLE 2. In-hospital outcomes: complications and outcomes of the study population during index hospitalization, as determined before and after propensity score matching

Variable	Before matching*				After matching†		
	Total (n = 1999)	Mitral valve repair (n = 424)	Mitral valve replacement (n = 1575)	*P*	Mitral valve repair (n = 352)	Mitral valve replacement (n = 352)	*P*
Categorical parameter							
Cardiogenic shock and need mechanical circulatory support	40 (2.0)	6 (1.4)	34 (2.2)	.332	6 (1.7)	6 (1.7)	1.000
New-onset any stroke	180 (9.0)	26 (6.1)	154 (9.8)	.020	23 (6.5)	40 (11.4)	.036
New-onset ischemic stroke	138 (6.9)	16 (3.8)	122 (7.7)	.004	13 (3.7)	30 (8.5)	.014
New-onset hemorrhagic stroke	54 (2.7)	11 (2.6)	43 (2.7)	.878	11 (3.1)	15 (4.3)	.557
Re-exploration for bleeding	52 (2.6)	13 (3.1)	39 (2.5)	.498	12 (3.4)	8 (2.3)	.503
Packed red blood cell transfusion >10 U	399 (20.0)	48 (11.3)	351 (22.3)	<.001	40 (11.4)	71 (20.2)	.002
De novo dialysis	151 (7.6)	17 (4.0)	134 (8.5)	.002	15 (4.3)	27 (7.7)	.065
Deep wound infection	28 (1.4)	3 (0.7)	25 (1.6)	.171	3 (0.9)	5 (1.4)	.727
In-hospital mortality	193 (9.7)	23 (5.4)	170 (10.8)	.001	22 (6.3)	38 (10.8)	.037
Continuous parameter							
Packed red blood cell transfusion, U	7.2 ± 7.8	5.0 ± 5.3	7.7 ± 8.3	<.001	5.1 ± 5.4	7.0 ± 7.2	<.001
Fresh frozen plasma, U	5.7 ± 7.6	4.0 ± 6.0	6.1 ± 7.9	<.001	4.2 ± 6.4	5.2 ± 6.4	.033
Platelets, U	11.8 ± 16.8	9.7 ± 14.6	12.3 ± 17.3	.004	9.9 ± 15.0	11.3 ± 16.6	.258
Intensive care unit stay, d	9.1 ± 12.0	5.7 ± 8.7	10.0 ± 12.6	<.001	5.9 ± 9.1	8.9 ± 12.0	<.001
In-hospital stay, d	38.6 ± 26.7	33.1 ± 23.0	40.1 ± 27.4	<.001	33.7 ± 23.3	39.1 ± 25.2	.003
In hospital cost, US$ $\times 10^3$	19.1 ± 10.2	15.8 ± 9.1	20.0 ± 10.3	<.001	16.0 ± 9.3	19.3 ± 10.4	<.001

*χ^2 Test for categorical variables and independent 2-sample *t* test for continuous variables. †McNemar test for categorical variables and paired sample *t* test for continuous variables.

streptococcal infections had contrary results (Figure E1). However, the differences were not statistically significant.

DISCUSSION

Since the first series in 1990,[24] cardiac surgeons worldwide have been attempting to answer the question of whether valve repair or replacement is better for patients with MV-IE; nevertheless, no solid conclusions have been reached. In retrospective studies that compared MV repair and replacement in patients with IE, patients in replacement groups were usually older, had more comorbidities, and were more critically ill preoperatively because of congestive heart failure or uncontrolled sepsis.[9,10,13] Hence, the outcomes were influenced not only by surgical procedures, but also by baseline conditions. However, conducting a randomized control trial is nearly impractical because of variable degrees of valve destruction, varying clinical conditions, and ethical concerns. To the best of our knowledge, this study is the first to compare MV repair and replacement for patients with IE using propensity score matching. With this method, we minimized differences in baseline patient conditions and hospital factors. Despite similar baseline characteristics, perioperative and late outcomes were significantly improved after MV repair than replacement in our study.

Repair Versus Replacement

The beneficial effect of MV repair can be attributed to 2 reasons. First, when the integrity of the mitral apparatus is preserved, left ventricular function is preserved more effectively.[25] Second, MV repair avoids the inherent risks of prosthetic heart valves. If a mechanical valve is implanted, thromboembolism or anticoagulant-induced hemorrhage might occur. If a bioprosthetic valve is used, structural deterioration is inevitable. Several studies have shown better short- and long-term outcomes after MV repair than replacement, even in elderly patients.[6,7,26,27]

Although not statistically significant, we showed the trend that MV repair is related to a reduction in readmission for heart failure, stroke, major bleeding, and redo MV surgery during follow-up. As an accumulation of all of the aforementioned events, the composite end point and

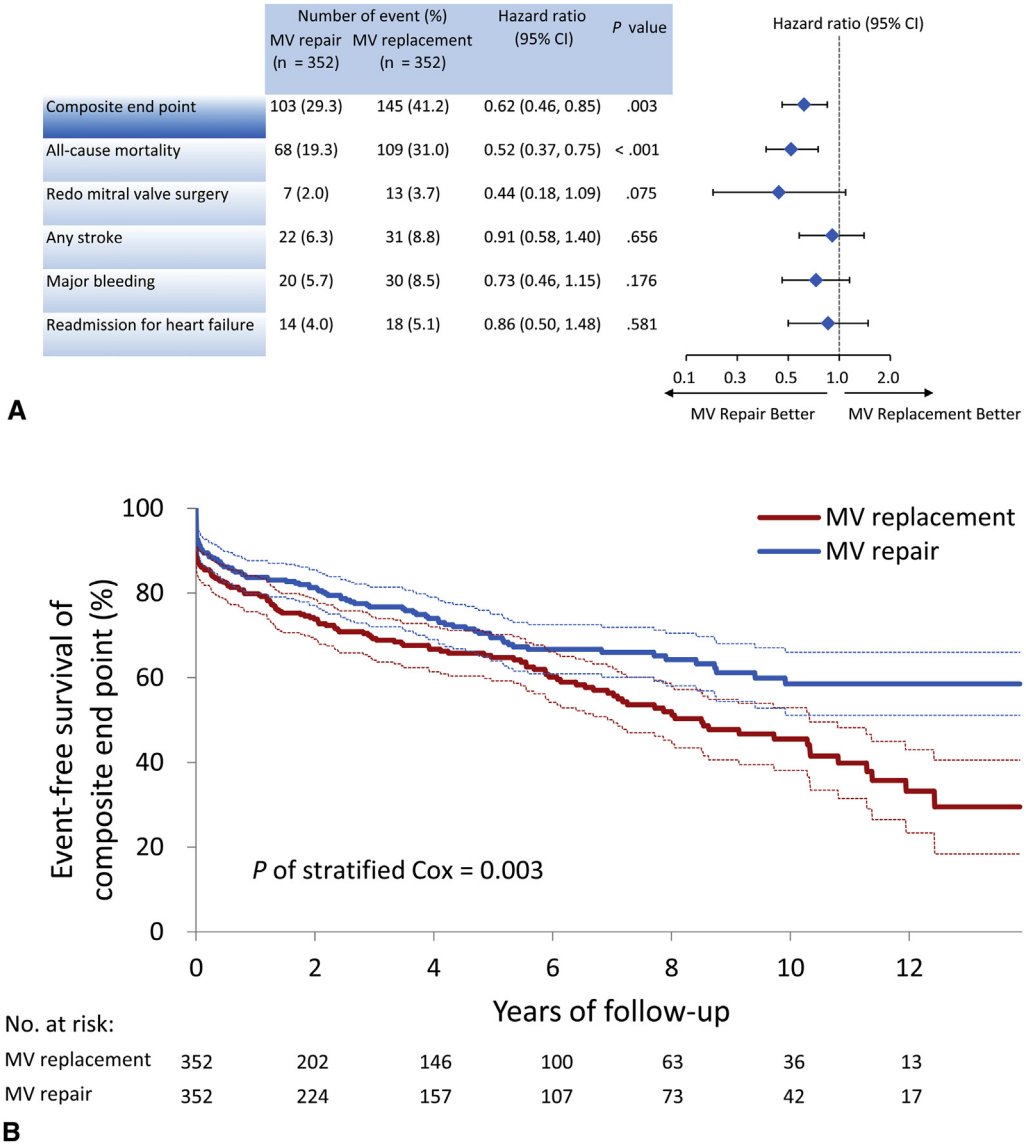


FIGURE 2. Late outcomes illustrated by a Forrest plot (A) and Kaplan–Meier curve (B) showing event-free survival during follow-up. *MV*, Mitral valve; *CI*, confidence interval.

all-cause mortality during follow-up were significantly lower in the MV repair group than in the MV replacement group. This finding indicates that MV repair provides greater improvements to late outcomes than MV replacement for IE patients.

Subgroup Analysis

Through subgroup analysis, we discovered that the beneficial effect of MV repair on the composite end point during follow-up was significant regardless of patient age, gender, or active or treated IE status. On the contrary, we found that patients who received surgery in hospitals with the highest valve surgery volumes benefited from MV repair significantly, whereas those who received surgery in the lowest volume hospitals did not. Moreover, in hospitals within the lowest MV repair volume quartile, patients who underwent MV replacement seemed to have lower numerical risk of the composite end point.

Published articles have indicated higher MV repair rates and lower mortality in high-volume centers than in low-volume centers.[28] In our study, the repair rates in centers with high MV repair volumes were significantly higher than those in centers with low volumes (54.0% vs 4.0%; $P < .01$). Furthermore, the outcomes of MV repair performed in low-volume hospitals did not outperform those of MV replacement. This finding supports our belief that for patients with IE, an experienced team specialized in MV repair surgery is crucial to a successful repair.

	Number of event (%)		Hazard ratio	*P* value
	MV repair (n = 352)	MV replacement (n = 352)	(95% CI)	
Age				.821
< 60 years	62 (24.9)	85 (34.8)	0.69 (0.50, 0.96)	
≥ 60 years	41 (39.8)	60 (55.6)	0.65 (0.44, 0.97)	
Gender				.390
Male	74 (30.0)	93 (37.8)	0.73 (0.54, 0.99)	
Female	29 (27.6)	52 (49.1)	0.57 (0.36, 0.90)	
Active IE				.441
No	19 (25.7)	35 (44.3)	0.55 (0.32, 0.97)	
Yes	84 (30.2)	110 (40.3)	0.71 (0.53, 0.94)	
Emergent surgery				.976
No	86 (27.1)	127 (39.3)	0.66 (0.50, 0.86)	
Yes	17 (48.6)	18 (62.1)	0.66 (0.34, 1.29)	
Stroke				.221
No	82 (27.1)	119 (39.9)	0.63 (0.48, 0.84)	
Yes	21 (42.9)	26 (48.1)	0.94 (0.53, 1.67)	
Atrial fibrillation				.608
No	78 (27.8)	111 (39.1)	0.69 (0.52, 0.92)	
Yes	25 (35.2)	34 (50.0)	0.59 (0.35, 0.99)	
GI bleeding				.49
No	80 (26.9)	119 (39.8)	0.64 (0.48, 0.85)	
Yes	23 (41.8)	26 (49.1)	0.80 (0.46, 1.40)	
Rheumatic heart history				.662
No	83 (27.5)	119 (39.9)	0.66 (0.50, 0.87)	
Yes	20 (40.0)	26 (48.1)	0.76 (0.42, 1.36)	
Mechanical AVR				.132
No	85 (27.1)	128 (40.9)	0.62 (0.47, 0.82)	
Yes	18 (47.4)	17 (43.6)	1.08 (0.56, 2.10)	
Additional valve surgery				.459
No	64 (26.0)	98 (38.6)	0.63 (0.46, 0.86)	
Yes	39 (36.8)	47 (48.0)	0.76 (0.50, 1.17)	
Any additional surgery				.709
No	88 (27.5)	128 (39.6)	0.67 (0.51, 0.88)	
Yes	15 (46.9)	17 (58.6)	0.58 (0.29, 1.17)	
Center volume of valve surgery				.925
Lowest volume quartile	15 (37.5)	16 (59.3)	0.63 (0.31, 1.27)	
Highest volume quartile	39 (24.5)	64 (38.8)	0.60 (0.40, 0.90)	
Center volume of MV repair surgery				.091
Lowest volume quartile	10 (58.8)	9 (60.0)	1.27 (0.51, 3.13)	
Highest volume quartile	45 (26.8)	78 (44.8)	0.55 (0.38, 0.79)	

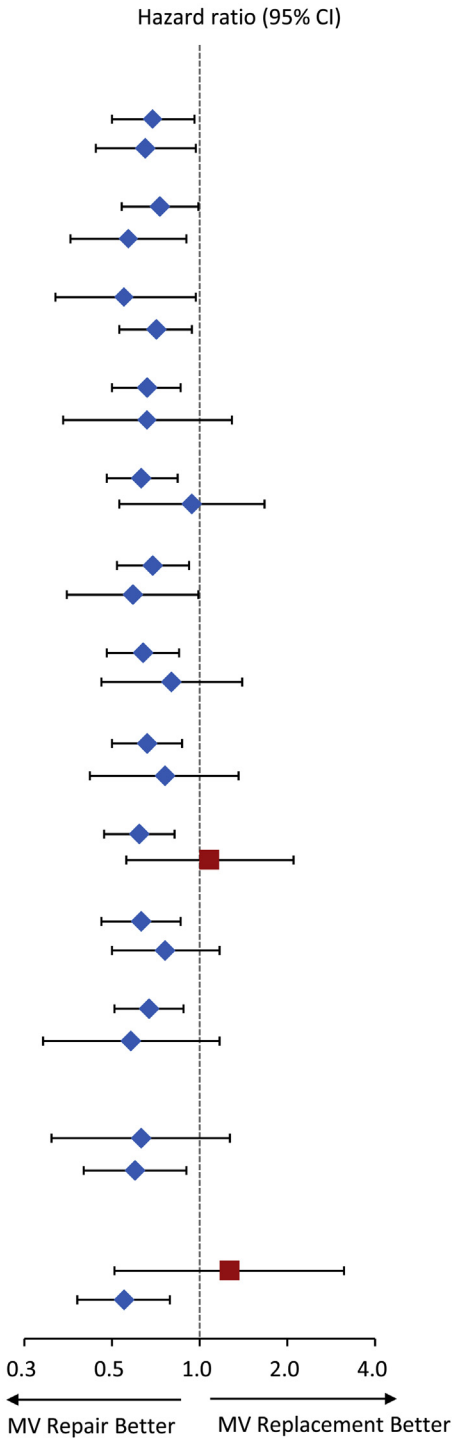


FIGURE 3. Forest plot showing risks of composite end point during follow-up in different subgroups. *MV*, Mitral valve; *CI*, confidence interval; *IE*, infective endocarditis; *GI*, gastrointestinal; *AVR*, aortic valve replacement.

MV Repair in the Real World

Despite the well known benefits of MV repair over replacement and guideline suggestions,[29] the proportion of MV repair in patients with IE remains low. Gammie et al reported a 29.7% frequency of MV repair for patients with IE between 1994 and 2003 in the United States.[8] During the same period, the MV repair rate was 45.7% in non-IE cases. Moreover, in the last year of their study period, the frequency rates of mitral repair for IE and non-IE patients were 34.5% and 59.8%, respectively.

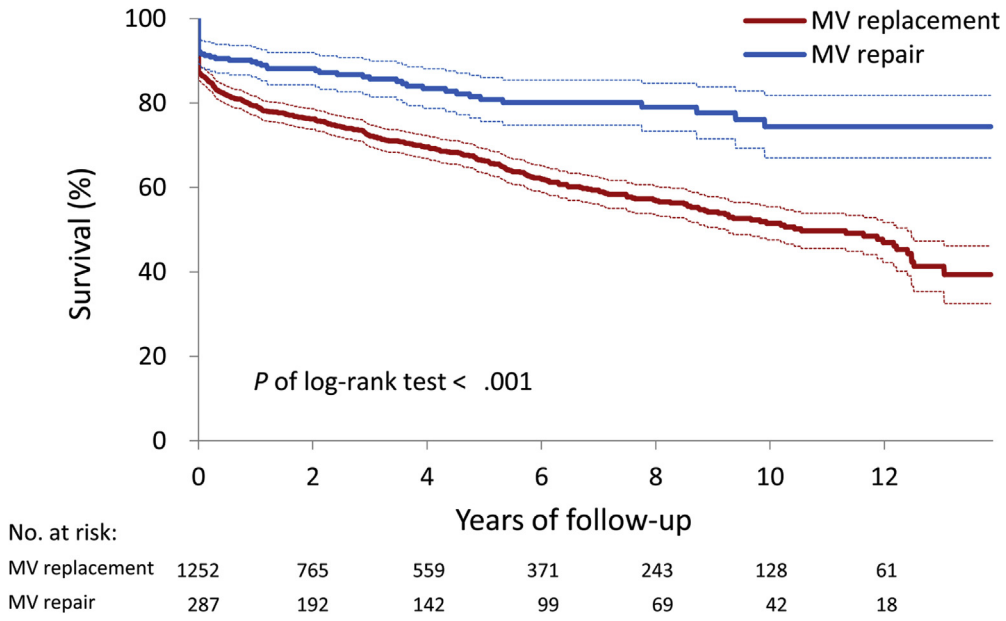


FIGURE 4. Kaplan–Meier curve showing late all-cause mortality of patients with active infective endocarditis. *MV*, Mitral valve.

In our study, the overall frequency of MV repair for IE in Taiwan during the 13-year period was 21.2%, and the frequency of MV repair in lowest-volume quartile hospitals was <10%. Although the proportion of MV repair has been increasing, it never exceeded 30% in our study period.

Unlike degenerative MV disease, endocarditis can cause severe destruction of leaflet and paravalvular structures, thus increasing the complexity and difficulty of valve repair. The frailty of the valve in patients with IE also raises concerns about the long-term durability of the repair. However, some authors have reported an MV repair rate of 75% to 82.7% in patients with IE with preferable results.[12,30-32] Because the benefit of MV repair in IE has been shown, a repair-first strategy for MV surgery must be incorporated for patients with IE; early referral to centers specialized in valve surgery can maximize the probability of successful repair and optimize patient outcome.

Study Limitations

This study has some limitations because of the administrative nature of the NHIRD. First, the diagnosis of IE was strictly on the basis of the ICD-9-CM system. Coding errors or misclassifications were possible. However, other studies have indicated that these codes are reliable substitutes for chart-based IE diagnosis on the basis of the revised Duke criteria.[33,34] Validation analysis also revealed good agreement between the coded IE diagnosis in Taiwan's NHIRD and that of clinically definite or possible IE in a tertiary center in Taiwan.[35] Furthermore, the type of MV surgery was doubly confirmed according to ICD-9-CM and NHI procedure codes. Therefore, we believe our study design to be reliable and the effects of code errors on our conclusions to be limited.

Second, several detailed clinical and surgical data are not available in the NHIRD, including lab data, ventricular ejection fraction, mitral regurgitation severity, heart failure symptoms, surgical indication and timing, antibiotics course, infection control status, MV repair techniques, and prosthetic valve brand and size, which might have influenced patient outcomes and our analysis. However, the NHI program has strict regulations regarding surgery, examination, and medication reimbursements. Comprehensive reviews of all medical records including imaging studies and lab data ensure that specific exams or interventions are granted only to patients who are indicated. Thus, national regulation by universal indication of treatment protocols could limit the potential bias of unavailable data.

Third, our study is observational in nature and the evidence level was limited by the database post hoc analysis. Despite adjustments for known confounders by using propensity score matching, unaddressed residual biases remain, including the aforementioned hemodynamics status, echocardiographic parameters, and extent of MV involvement. MV replacement might be more likely to be performed in cases in which the valve is more severely affected and the larger extent of the disease rather than the procedure itself can explain worse outcomes. Therefore, we could only investigate associations but could not infer causation.

CONCLUSIONS

According to this nationwide population-based propensity score-matching study, MV repair for patients with IE

Nationwide Cohort Study of Mitral Valve Repair Versus Replacement for Infective Endocarditis

Division of Thoracic and Cardiovascular Surgery
Chang-Gung Memorial Hospital, Linko, Taiwan
First author: Hsiu-An Lee
Corresponding author: Shao-Wei Chen

VIDEO 1. The study's lead author speaks about the study's purpose, results, and conclusion of its findings. Video available at: https://www.jtcvs.org/article/S0022-5223(18)31051-1/fulltext.

has better perioperative and late outcomes compared with MV replacement. However, the beneficial effects of MV repair are uncertain in hospitals with lower MV repair volumes. Therefore, MV repair performed by an experienced team specialized in valve surgery rather than MV replacement is recommended for IE patients whenever possible, even with an active infection status (Video 1).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

This study was on the basis of data from the NHIRD provided by the National Health Insurance Administration of the Ministry of Health and Welfare, Taiwan, and managed by the National Health Research Institutes of Taiwan. However, the interpretations and conclusions contained herein do not represent those of the National Health Insurance Administration, Ministry of Health and Welfare, or the National Health Research Institute of Taiwan. Drs S.-W. Chen and H.-A. Lee had full access to all data used in the study and take responsibility for the integrity of the data and the accuracy of the analysis.

The authors thank Alfred Hsing-Fen Lin and Zoe Ya-Jhu Syu for their assistance with the statistical analysis.

References

1. Shih CJ, Chu H, Chao PW, Lee YJ, Kuo SC, Li SY, et al. Long-term clinical outcome of major adverse cardiac events in survivors of infective endocarditis: a nationwide population-based study. *Circulation*. 2014;130:1684-91.
2. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med*. 2001;345:1318-30.
3. Chu VH, Cabell CH, Benjamin DK Jr, Kuniholm EF, Fowler VG Jr, Engemann J, et al. Early predictors of in-hospital death in infective endocarditis. *Circulation*. 2004;109:1745-9.
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2014;129:e521-643.
5. David TE, Ivanov J, Armstrong S, Christie D, Rakowski H. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. *J Thorac Cardiovasc Surg*. 2005;130:1242-9.
6. Chikwe J, Goldstone AB, Passage J, Anyanwu AC, Seeburger J, Castillo JG, et al. A propensity score-adjusted retrospective comparison of early and mid-term results of mitral valve repair versus replacement in octogenarians. *Eur Heart J*. 2011;32:618-26.
7. Vassileva CM, Mishkel G, McNeely C, Boley T, Markwell S, Scaife S, et al. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. *Circulation*. 2013;127:1870-6.
8. Gammie JS, Sheng S, Griffith BP, Peterson ED, Rankin JS, O'Brien SM, et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons adult cardiac surgery database. *Ann Thorac Surg*. 2009;87:1431-7; discussion 1437-9.
9. Ruttmann E, Legit C, Poelzl G, Mueller S, Chevtchik O, Cottogni M, et al. Mitral valve repair provides improved outcome over replacement in active infective endocarditis. *J Thorac Cardiovasc Surg*. 2005;130:765-71.
10. Feringa HH, Shaw LJ, Poldermans D, Hoeks S, van der Wall EE, Dion RA, et al. Mitral valve repair and replacement in endocarditis: a systematic review of literature. *Ann Thorac Surg*. 2007;83:564-70.
11. Shang E, Forrest GN, Chizmar T, Chim J, Brown JM, Zhan M, et al. Mitral valve infective endocarditis: benefit of early operation and aggressive use of repair. *Ann Thorac Surg*. 2009;87:1728-33; discussion: 1734.
12. de Kerchove L, Vanoverschelde JL, Poncelet A, Glineur D, Rubay J, Zech F, et al. Reconstructive surgery in active mitral valve endocarditis: feasibility, safety and durability. *Eur J Cardiothorac Surg*. 2007;31:592-9.
13. Jung SH, Je HG, Choo SJ, Song H, Chung CH, Lee JW. Surgical results of active infective native mitral valve endocarditis: repair versus replacement. *Eur J Cardiothorac Surg*. 2011;40:834-9.
14. Chang JJ, Lin MS, Chen TH, Chen DY, Chen SW, Hsu JT, et al. Heart failure and mortality of adult survivors from acute myocarditis requiring intensive care treatment - a nationwide cohort study. *Int J Med Sci*. 2017;14:1241-50.
15. Chen SW, Tsai FC, Lin YS, Chang CH, Chen DY, Chou AH, et al. Long-term outcomes of extracorporeal membrane oxygenation support for postcardiotomy shock. *J Thorac Cardiovasc Surg*. 2017;154:469-77.e2.
16. Chou AH, Chen TH, Chen CY, Chen SW, Lee CW, Liao CH, et al. Long-term outcome of cardiac surgery in 1,040 liver cirrhosis patient- nationwide population-based cohort study. *Circ J*. 2017;81:476-84.
17. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA*. 2012;308:1906-14.
18. Cheng CL, Chien HC, Lee CH, Lin SJ, Yang YH. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in national health insurance research database in Taiwan. *Int J Cardiol*. 2015;201:96-101.
19. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172:1092-7.
20. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10:150-61.
21. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399-424.
22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
23. Shinozaki T, Matsuyama Y. Brief report: doubly robust estimation of standardized risk difference and ratio in the exposed population. *Epidemiology*. 2015;26:873-7.
24. Dreyfus G, Serraf A, Jebara VA, Deloche A, Chauvaud S, Couetil JP, et al. Valve repair in acute endocarditis. *Ann Thorac Surg*. 1990;49:706-11; discussion: 712-3.
25. David TE, Uden DE, Strauss HD. The importance of the mitral apparatus in left ventricular function after correction of mitral regurgitation. *Circulation*. 1983;68:II76-82.
26. Toyoda N, Itagaki S, Egorova NN, Tannous H, Anyanwu AC, El-Eshmawi A, et al. Real-world outcomes of surgery for native mitral valve endocarditis. *J Thorac Cardiovasc Surg*. 2017;154:1906-12.e9.
27. Bakaeen FG, Shroyer AL, Zenati MA, Badhwar V, Thourani VH, Gammie JS, et al. Mitral valve surgery in the US veterans administration health system: 10-year outcomes and trends. *J Thorac Cardiovasc Surg*. 2018;155:105-17.e5.

28. Vassileva CM, Boley T, Markwell S, Hazelrigg S. Impact of hospital annual mitral procedural volume on mitral valve repair rates and mortality. *J Heart Valve Dis*. 2012;21:41-7.
29. AATS Surgical Treatment of Infective Endocarditis Consensus Guidelines Writing Committee Chairs, Pettersson GB, Coselli JS, Writing Committee, Pettersson GB, Coselli JS, et al. 2016 The American Association for Thoracic Surgery (AATS) consensus guidelines: surgical treatment of infective endocarditis: executive summary. *J Thorac Cardiovasc Surg*. 2017;153:1241-58.e29.
30. Iung B, Rousseau-Paziaud J, Cormier B, Garbarz E, Fondard O, Brochet E, et al. Contemporary results of mitral valve repair for infective endocarditis. *J Am Coll Cardiol*. 2004;43:386-92.
31. Zegdi R, Debieche M, Latremouille C, Lebied D, Chardigny C, Grinda JM, et al. Long-term results of mitral valve repair in active endocarditis. *Circulation*. 2005;111:2532-6.
32. Kanemitsu H, Nakamura K, Fukunaga N, Koyama T. Long-term outcomes of mitral valve repair for active endocarditis. *Circ J*. 2016;80:1148-52.
33. Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veterans Affairs hospital discharge databases coded serious bacterial infections accurately. *J Clin Epidemiol*. 2007;60:397-409.
34. Heiro M, Helenius H, Hurme S, Savunen T, Metsarinne K, Engblom E, et al. Long-term outcome of infective endocarditis: a study on patients surviving over one year after the initial episode treated in a Finnish teaching hospital during 25 years. *BMC Infect Dis*. 2008;8:49.
35. Chen SJ, Chao TF, Lin YJ, Lo LW, Hu YF, Tuan TC, et al. Cool seasons are related to poor prognosis in patients with infective endocarditis. *Int J Biometeorol*. 2012;56:973-81.

Key Words: endocarditis, mitral valve surgery, mitral valve repair, mitral valve replacement

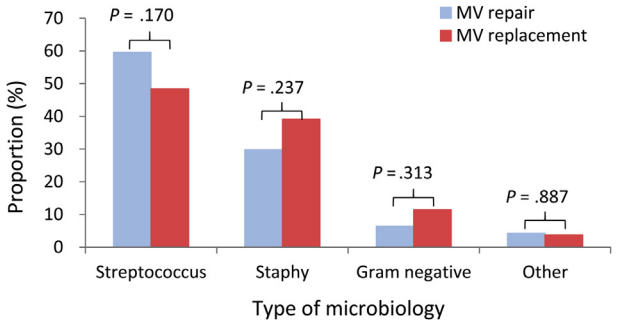


FIGURE E1. Microbiology of patients who underwent mitral valve (*MV*) surgery during active infective endocarditis.

TABLE E1. Primary outcomes during follow-up, as determined using a doubly robust estimator (sensitivity analysis)

Outcome	Event, n (%)		Risk difference*: MV replacement - MV repair		
	MV repair (n = 352)	MV replacement (n = 352)	Mean	Variance	SD
All-cause mortality	68 (19.3)	109 (31.0)	0.0270	0.0088	0.0936
Composite end point†	103 (29.3)	145 (41.2)	0.0196	0.0022	0.0468
Redo mitral valve surgery	7 (2.0)	13 (3.7)	0.0303	0.2135	0.4621
Any stroke	22 (6.3)	31 (8.8)	0.0311	0.0691	0.2628
Major bleeding	20 (5.7)	30 (8.5)	0.0344	0.1499	0.3872
Readmission for heart failure	14 (4.0)	18 (5.1)	0.0349	0.2599	0.5098

MV, Mitral valve. *Estimated survival probability at 14-year follow-up. †Composite end point, comprising 1 or more of the following: redo mitral valve surgery, stroke, major bleeding, readmission for heart failure, and all-cause mortality.

TABLE E2. New-onset stroke during index hospitalization and primary outcomes during follow-up, stratified according to study group

Outcome	Event, n (%)			OR or HR (95% CI), *P* value					
	Repair (n = 352)	Replacement with mechanical valve (n = 221)	Replacement with bioprosthetic valve (n = 131)	Repair vs replacement with mechanical valve		Repair vs replacement with bioprosthetic valve		Replacement with mechanical valve vs replacement with bioprosthetic valve	
				OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Complications during index hospitalization									
New-onset any stroke	23 (6.5)	25 (11.3)	15 (11.5)	0.55 (0.30-0.99)	.047	0.54 (0.27-1.07)	.078	0.99 (0.50-1.95)	.969
New-onset ischemic stroke	13 (3.7)	17 (7.7)	13 (9.9)	0.46 (0.22-0.97)	.041	0.35 (0.16-0.77)	.009	0.76 (0.36-1.61)	.470
New-onset hemorrhagic stroke	11 (3.1)	10 (4.5)	5 (3.8)	0.68 (0.28-1.63)	.388	0.81 (0.28-2.39)	.706	1.20 (0.40-3.57)	.751
Primary outcomes during follow-up									
Composite end point*	103 (29.3)	93 (42.1)	52 (39.7)	0.72 (0.54-0.95)	.019	0.60 (0.43-0.83)	.002	0.83 (0.59-1.17)	.296
All-cause mortality	68 (19.3)	68 (30.8)	41 (31.3)	0.64 (0.46-0.90)	.009	0.51 (0.35-0.76)	<.001	0.80 (0.54-1.18)	.266
Redo mitral valve surgery†	7 (2.0)	7 (3.2)	6 (4.6)	0.69 (0.25-1.96)	.489	0.38 (0.13-1.14)	.084	0.55 (0.19-1.61)	.277
Any stroke†	22 (6.3)	25 (11.3)	6 (4.6)	0.61 (0.35-1.07)	.086	1.19 (0.48-2.95)	.705	1.96 (0.81-4.72)	.136
Major bleeding†	20 (5.7)	23 (10.4)	7 (5.3)	0.59 (0.33-1.07)	.082	0.95 (0.40-2.25)	.907	1.61 (0.69-3.74)	.268
Readmission for heart failure†	14 (4.0)	12 (5.4)	6 (4.6)	0.82 (0.38-1.77)	.608	0.77 (0.30-1.98)	.585	0.94 (0.36-2.48)	.900

OR, Odds ratio; *HR*, hazard ratio; *CI*, confidence interval. *Composite end point, comprising 1 or more of the following: redo mitral valve surgery, stroke, major bleeding, re-admission for heart failure, and all-cause mortality. †Compared using a subdistribution hazard model in which all-cause mortality was considered to be a competing risk.

TABLE E3. Baseline characteristics of patients with active IE and treated IE

Variable	Total (N = 1999)	Active IE (n = 1539)	Treated IE (n = 460)	ASMD
Surgery type				
Mitral valve repair	424 (21.2)	287 (18.6)	137 (29.8)	0.262
Mitral valve replacement	1575 (78.8)	1252 (81.4)	323 (70.2)	0.262
Age, y	51.8 ± 15.9	51.0 ± 16.3	54.3 ± 14.0	0.221
Age group				
<40 y	499 (25.0)	423 (27.5)	76 (16.5)	0.267
40-59 y	842 (42.1)	630 (40.9)	212 (46.1)	0.104
≥60 y	658 (32.9)	486 (31.6)	172 (37.4)	0.123
Male gender	1337 (66.9)	1023 (66.5)	314 (68.3)	0.038
Comorbid conditions				
Stroke	277 (13.9)	196 (12.7)	81 (17.6)	0.136
Diabetes mellitus	355 (17.8)	279 (18.1)	76 (16.5)	0.042
Hypertension	611 (30.6)	432 (28.1)	179 (38.9)	0.231
Heart failure	526 (26.3)	293 (19.0)	233 (50.7)	0.703
Coronary arterial disease	406 (20.3)	278 (18.1)	128 (27.8)	0.234
Atrial fibrillation	378 (18.9)	185 (12.0)	193 (42.0)	0.716
Dialysis	109 (5.5)	101 (6.6)	8 (1.7)	0.244
Chronic obstructive pulmonary disease	98 (4.9)	69 (4.5)	29 (6.3)	0.081
Liver cirrhosis	98 (4.9)	73 (4.7)	25 (5.4)	0.031
Gastrointestinal bleeding history	340 (17.0)	252 (16.4)	88 (19.1)	0.072
Drug abuse	45 (2.3)	39 (2.5)	6 (1.3)	0.090
Charlson total score	2.0 ± 2.1	1.9 ± 2.1	2.2 ± 2.1	0.128

IE, Infective endocarditis; *ASMD*, absolute standardized mean difference.