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ORIGINAL ARTICLE
Valvular Heart Disease

Isolated Tricuspid Regurgitation and Long-Term Outcome in Patients With Preserved Ejection Fraction

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Background: The aim of this study was to evaluate the association of isolated tricuspid regurgitation (TR) with long-term outcome in patients with preserved left ventricular ejection fraction (LVEF).

Methods and Results: We retrospectively analyzed 3,714 patients who had undergone both scheduled transthoracic echocardiography and electrocardiography in 2013 in a hospital-based population, after excluding severe and moderate left-side valvular disease and LVEF <50%. We classified patients into 2 groups: moderate to severe TR (n=53) and no moderate to severe TR (n=3,661). Next, we generated a propensity score (PS)-matched cohort: the moderate to severe TR group and the no moderate to severe TR group (n=41 in each group). The primary outcome was a composite of all-cause death and major adverse cardiac events. In the moderate to severe TR group, patients were older, and more likely to have higher left atrial volume index and E/e' than those in the no moderate to severe TR group. In the PS-matched cohort, cumulative 3-year incidence of the primary outcome was 61.5% in the moderate to severe TR group and 24.3% in the no moderate to severe TR group (log-rank P=0.043; hazard ratio, 2.86; 95% CI: 1.37–6.37).

Conclusions: Isolated moderate to severe TR is associated with poor clinical outcome in patients with preserved LVEF.

Key Words: Ejection fraction; Prognosis; Tricuspid valve

Tricuspid regurgitation (TR) is a common condition,[1] especially in the elderly. The association of TR with long-term outcomes has been shown to be significant in large heterogeneous groups[2] and in a meta-analysis,[3] suggesting that intervention to tricuspid valve may lead to survival benefits. Mitral or aortic valve disease, and reduced left ventricular ejection fraction (LVEF), however, affect the tricuspid valve, mortality, and morbidity. A large meta-analysis of TR may address the concern that TR may be a surrogate marker of comorbid heart disease using extensive adjustment,[3] but very few studies on isolated TR, defined as TR without decreased LVEF or severe left-sided valvular disease, were included in that analysis.[4–6] Thus, we confined the present analysis to the case of isolated TR in patients without decreased LVEF or severe left-sided valvular disease and assessed whether isolated TR is an independent indicator of outcome.

Methods

Subjects

We retrospectively analyzed 4,444 patients who had undergone simultaneous scheduled transthoracic echocardiography (TTE) and electrocardiography (ECG) at Kitano Hospital in 2013 at the physician's discretion.[7–10] Subject selection is shown in **Figure 1**. We excluded patients with severe or moderate aortic stenosis (n=133), aortic regurgitation (n=133), mitral stenosis (n=9), mitral regurgitation (n=169), severe congenital heart disease or pericardial disease (n=0), or LVEF <50% (n=407) due to the effects of these conditions on TR. The study population consisted of 3,714 patients, who were categorized into 2 groups depending on the presence or absence of moderate to severe TR (**Figure 1**): the moderate to severe TR group (n=53) and the no moderate to severe TR group (n=3,661).

The research protocol was approved by the Institutional Review Board of Kitano Hospital (approval number: P16-02-005). Informed consent was waived due to the retrospective design of the study. We disclosed the details of the present study to the public as an opt-out method and the notice clearly informed patients of their right to refuse enrollment. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's Human Research Committee. Patient records and information were anonymized and de-identified before analysis.[7–10]

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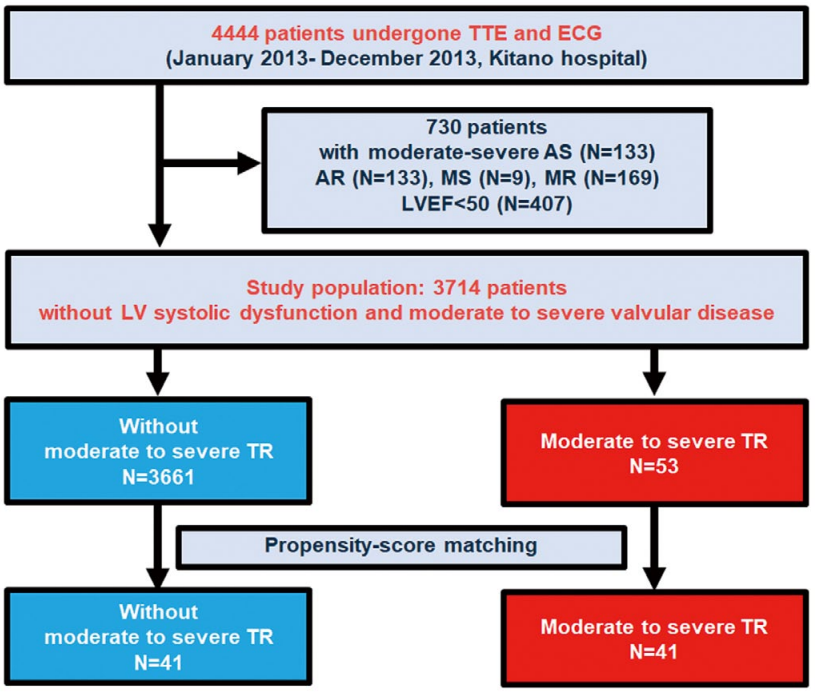


Figure 1. Flowchart of subject selection. AR, aortic regurgitation; AS, aortic stenosis; ECG, electrocardiography; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Data Collection

All patients underwent TTE by expert sonographers (level 3 according to the definitions of the American Society of Echocardiography) and the echocardiography parameters were interpreted by experienced attending physicians at the echocardiography laboratory.[11,12] An integrative, semiquantitative approach as recommended by the American Society of Echocardiography[13] was used for evaluation of TR. First, the severity of valve regurgitation by evaluating specific signs that would point to either less than mild or severe regurgitation was assessed. TR was evaluated on apical 4-chamber view, parasternal short-axis view at the level of the aortic valve, right ventricular (RV) inflow view, and subxiphoid view. Specific signs included color jet area, vena contracta width, density of continuous Doppler jet, hepatic vein flow pattern, transtricuspid inflow pattern, annular diameter, and right heart size. If all of the indices and signs were concordant, we defined TR as less than mild or severe. If the qualitative or semiquantitative parameters were in the intermediate range between mild and severe, we defined TR as at least moderate to severe if the majority of the signs and indices were concordant with severe TR.[13]

Using the TTE database, we extracted data regarding wall thickness, LV diastolic dimensions, LV systolic dimensions, left atrial (LA) diameter, LA volume index (LAVI), LVEF, and body mass index (BMI). From the ECG database, we extracted data on cardiac rhythm and recorded them as they were documented; therefore, we could not determine whether atrial fibrillation (AF) was paroxysmal or persistent.[7] Based on the TTE data along with the catheter suite's database, we identified patients who had previous myocardial infarction. Any disagreements were resolved by consensus. LV mass index (LVMI) and relative wall thickness (RWT) were calculated using the formula recommended by the American Society of Echocardiography.[14] We defined high RWT as >0.42. High LVMI was defined as >115 g/m^2 for male patients and >95 g/m^2 for female patients. Septal e' was measured on apical 4-chamber view and E/e' was calculated at the interventricular septum. We defined normal e' as ≥7 cm/s and low e' as <7 cm/s, and normal E/e' as ≤14 and high E/e' as >14 according to the American Society of Echocardiography guidelines.[15] High LAVI was defined as >34 mL/m^2. Pulmonary systolic pressure was calculated as follows: first, RV systolic pressure was determined from the TR jet velocity using the simplified Bernoulli equation; second, right atrial pressure was estimated according to the diameter and collapsibility of the inferior vena cava (the diameter of inferior vena cava), and this was added to the calculated gradient to yield pulmonary systolic pressure.[16] e' was measured on apical 4-chamber view at the interventricular septum. Data from 2-D TTE were analyzed at baseline. LVEF was measured using the Teichholz method or modified Simpson rule. All TTE measurements were determined using the average of at least 3 cardiac cycles.

We extracted patient information from the electronic medical records at the present institution, including age, sex, and type of disease (i.e., ischemic heart disease, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Edition [ICD-10] codes I20–I25; hypertension, ICD-10 codes I10–I15; dyslipidemia, ICD-10 code E78; diabetes mellitus, ICD-10 codes E10–E14; and chronic kidney disease [CKD], ICD-10 code N18). Follow-up data from serial clinic visits during June 2017 were also collected retrospectively from electronic medical records.[7–10]

Outcome Measures

The primary outcome was a composite of all-cause death and major adverse cardiac events (MACE), defined as acute heart failure, acute myocardial infarction, unstable

Table. Baseline Subject Characteristics and Transthoracic Echocardiography

	Entire cohort			PS-matched cohort		
	No moderate to severe TR (n=3,661)	Moderate to severe TR (n=53)	P-value†	No moderate to severe TR (n=41)	Moderate to severe TR (n=41)	P-value†
Clinical characteristics						
Age (years)‡	69 (58–77)	80 (73.5–84)	<0.001	80 (72–83.5)	81 (74.5–85.5)	0.32
Male‡	1,970 (53.8)	25 (47.2)	0.34	19 (46.3)	21 (51.2)	0.66
BMI (kg/m^2)	23.3±4.8	21.1±3.5	<0.001	22.6±3.4	21.4±3.7	0.14
BMI>25	1,062 (29.2)	5 (9.6)	0.0020	12 (29.3)	5 (12.2)	0.057
BMI>30	203 (5.6)	2 (3.9)	0.59	1 (2.4)	2 (4.9)	0.56
Diabetes‡	1,114 (30.4)	18 (34.0)	0.58	20 (48.9)	15 (36.6)	0.26
Hypertension‡	2,033 (55.5)	35 (66.0)	0.13	23 (56.1)	27 (65.9)	0.37
Dyslipidemia‡	1,114 (30.4)	12 (22.6)	0.22	9 (22.0)	9 (22.0)	1.00
Ischemic heart disease‡	1,058 (28.9)	17 (32.1)	0.61	16 (39.0)	15 (36.6)	0.82
Chronic kidney disease‡	481 (13.1)	9 (17.0)	0.41	7 (17.1)	8 (19.5)	0.78
Atrial fibrillation‡	314 (8.6)	28 (52.8)	<0.001	24 (58.5)	21 (51.2)	0.51
Echocardiography parameters						
LV diastolic dimension (cm)	4.61±0.52	4.42±0.55	0.0026	4.63±0.50	4.43±0.53	0.048
LV systolic dimension (cm)	3.04±0.38	2.93±0.50	0.022	3.05±0.33	2.93±0.49	0.078
Diastolic IST (cm)	0.82±0.17	0.86±0.17	0.054	0.81±0.10	0.85±0.14	0.18
Diastolic LV PWT (cm)	0.80±0.14	0.84±0.15	0.091	0.80±0.10	0.83±0.14	0.55
RWT	0.35±0.07	0.38±0.06	<0.001	0.35±0.05	0.38±0.06	0.023
High RWT§	482 (13.2)	15 (28.3)	0.0013	4 (9.8)	11 (26.8)	0.046
LVMI (g/m^2)	75.6±21.4	83.6±29.8	0.069	77.8±14.8	81.8±28.1	0.92
High LVMI¶	322 (8.8)	10 (19.2)	0.0091	2 (4.9)	5 (12.2)	0.24
Left atrial dimension (cm)	3.50±0.64	4.05±0.95	<0.001	4.03±0.65	4.00±0.93	0.81
LAVI (mL/m^2)	22.4±10.7	37.2±19.2	<0.001	34.4±14.1	37.8±19.7	0.55
High LAVI‡,††	332 (10.0)	25 (54.4)	<0.001	22 (53.7)	23 (56.1)	0.82
EF (%)‡	63.1±4.2	62.7±5.6	0.51	63.0±3.6	62.6±5.5	0.87
Cardiac index (L/min/m^2)	2.73±0.80	2.90±0.80	0.080	3.16±1.09	2.89±0.83	0.43
E (cm/s)	72.3±20.3	88.7±38.4	<0.001	87.7±24.3	85.6±28.9	0.59
A (cm/s)	79.1±27.0	88.1±32.1	0.21	92.1±23.0	87.5±32.4	0.28
E/A	0.97±0.43	0.89±0.52	0.12	0.93±0.68	0.91±0.57	0.66
Dec time (ms)	225.0±61.2	216.4±66.9	0.16	204.2±67.5	217.5±64.2	0.27
e' (cm/s)	7.1±2.6	6.6±2.3	0.33	7.1±2.1	6.5±2.3	0.21
a' (cm/s)	9.3±2.3	9.0±2.7	0.76	8.8±2.5	8.6±2.5	0.92
E/e'	11.1±4.3	14.0±5.5	<0.001	13.2±4.3	14.2±5.2	0.51
E/e'>14‡	689 (19.5)	19 (39.6)	<0.001	17 (41.5)	17 (41.5)	1.00
Heart rate (beats/min)	70.9±15.0	76.6±16.0	0.0095	77.7±18.6	76.7±17.1	0.98
TRPG (mmHg)	29.9±10.9	53.1±33.4	<0.001	28.1±6.5	57.0±37.1	<0.001
SPAP (mmHg)	35.0±11.6	60.8±35.3	<0.001	32.3±7.4	64.0±39.4	<0.001

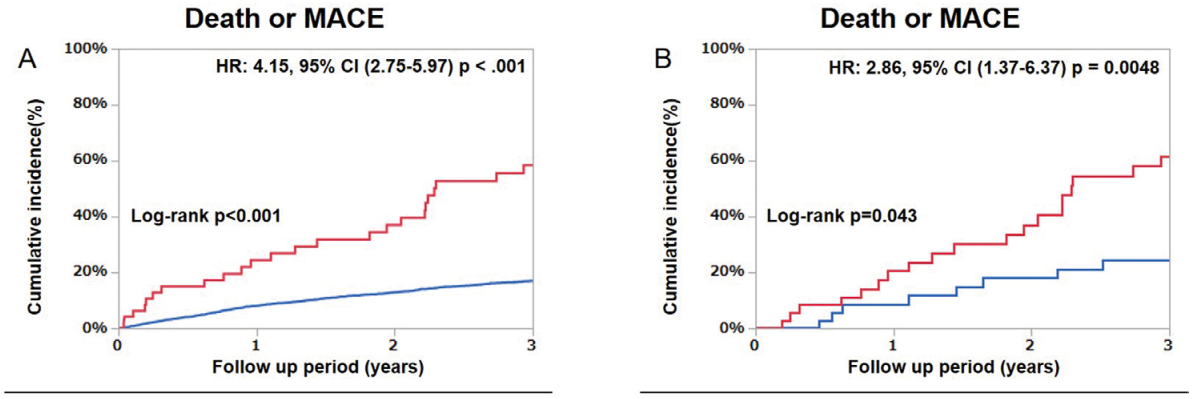
Data given as n (%), mean±SD or median (IQR). †Chi-squared test or Fisher's exact test for categorical variables, and Student's t-test or Wilcoxon rank sum test for continuous variables. ‡Variables relevant to moderate to severe TR selected for logistic regression modeling to develop the propensity score for moderate to severe TR. §>0.42. ¶>115 g/m^2 for male patients and >95 g/m^2 for female patients. ††>34 mL/m^2. A, transmitral late peak velocity; a', late diastolic mitral annular velocity; BMI, body mass index; E, transmitral early peak velocity; e', early diastolic mitral annular velocity; EF, ejection fraction; IST, interventricular septum thickness; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; PS, propensity score; PWT, posterior wall thickness; RWT, relative wall thickness; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; TRPG, tricuspid regurgitant pressure gradient.

angina pectoris, cerebral infarction, cerebral hemorrhage, and emerging aorta and peripheral vascular disease, including treatment for aortic aneurysm. The hospitalization for surgery of TR was not observed before the incidence of primary endpoints.

Statistical Analysis

Categorical variables are presented as n (%). They were compared using the chi-squared test or Fisher's exact test. Continuous variables are expressed as mean±SD or median (IQR). Based on their distributions, the continuous variables were compared using the Student t-test or Wilcoxon rank-sum test.

To balance the baseline clinical characteristics associated with moderate to severe TR, we used a propensity score (PS)-matched cohort design (**Supplementary Table**). A logistic regression model was developed to construct the PS for moderate to severe TR with 11 baseline clinical variables: age, LVEF (as continuous variables), and sex, and the history of diabetes mellitus, hypertension, dyslipidemia,



Interval (Years)	0	1	2	3
Moderate to severe TR				
N of patients with at least 1 event		11	16	24
N of patients at risk	53	32	25	16
Cumulative incidence		24.4%	36.9%	58.3%
No moderate to severe TR				
N of patients with at least 1 event		253	389	495
N of patients at risk	3661	2730	2345	2020
Cumulative incidence		8.0%	12.8%	16.9%

Interval (Years)	0	1	2	3
Moderate to severe TR				
N of patients with at least 1 event		7	12	19
N of patients at risk	41	26	19	12
Cumulative incidence		20.5%	37.0%	61.5%
No moderate to severe TR				
N of patients with at least 1 event		3	6	8
N of patients at risk	41	31	27	24
Cumulative incidence		8.6%	18.0%	24.3%

Figure 2. Cumulative incidence of the primary outcome (composite of all-cause death and major adverse cardiac events [MACE]) in the (**A**) entire cohort and (**B**) propensity score-matched cohort. HR, hazard ratio; TR, tricuspid regurgitation.

ischemic heart disease, CKD, AF, high LAVI, high LVMI, high E/e' (**Table**). The C statistic was 0.86 and the coefficients of the independent variables are given in **Supplementary Table**. PS was calculated by summing all coefficients multiplies corresponding variables. Based on the estimated PS, patients in the no moderate to severe TR group were matched to those in the moderate to severe TR group by nearest-neighbor matching, with a caliper of 0.2. The distribution of PS in both groups is shown in **Supplementary Figure 1**.

Next, we compared the 3-year clinical outcomes between the moderate to severe TR group and the no moderate to severe TR group in the entire and the PS-matched cohort. Cumulative incidences of clinical events were estimated using the Kaplan-Meier method, and the intergroup differences were assessed using the log-rank test. Cox proportional hazards models were used to estimate the risk of primary and secondary outcomes associated with moderate to severe TR relative to no moderate to severe TR. Proportional hazard assumptions for the moderate to severe TR group and the no moderate to severe TR group were assessed using plots of log (time) vs. log [−log (survival)] stratified by variable, and were verified as acceptable.

All statistical analysis was conducted by physicians (Y.S. and T.K.) using JMP version 14 (SAS Institute, Chicago, IL, USA). All reported P-values were 2-tailed, and P<0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 53 patients had moderate to severe TR, whereas 3,661 patients had no moderate to severe TR (**Figure 1**). Baseline subject characteristics are listed in **Table**. Compared with the no moderate to severe TR group, the patients with moderate to severe TR were older, and were more likely to have a smaller BMI, high RWT, high LVMI, high LAVI, high E/e', and a high systolic pulmonary artery pressure (SPAP; **Table**). After the PS matching, 41 patients with no moderate to severe TR were matched to 41 patients with moderate to severe TR. In the PS-matched cohort, the baseline clinical characteristics were well balanced between the 2 groups (**Table**). The trend of differences in the echocardiography parameters in the PS-matched cohort was generally consistent with that in the entire cohort.

Clinical Outcomes

Median follow-up duration after the index echocardiography was 1,280 days (IQR, 434–1470 days), with a follow-up rate of 80.4% at 1 year, 72.3% at 2 years, and 64.6% at 3 years. The cumulative 3-year incidence of the primary outcome measure was significantly higher in the moderate to severe TR group than in the no moderate to severe TR group (**Figure 2A**; 58.3% vs. 16.9%, log-rank P<0.0001). The excess risk of primary outcome measure in the moderate to severe TR group relative to that in the no moderate to severe TR group was significant (HR, 4.15; 95% CI: 2.75–5.97, P<0.001). In the PS-matched cohort, the cumulative 3-year incidence of the primary outcome measure was significantly higher in the moderate to severe TR group than in the no moderate to severe TR group (**Figure 2B**; 61.5% vs. 24.3%, log-rank P=0.043). The excess risk of primary outcome measures in the moderate to severe TR group relative to that in the no moderate to severe TR group remained significant (HR, 2.86; 95% CI: 1.37–6.37, P=0.0048).

Moderate to Severe TR Stratified on High SPAP and AF

When we stratified the moderate to severe TR group into 2 groups according to SPAP ≥60 mmHg, there was no significant difference in the cumulative incidence of primary outcomes between the groups (log-rank P=0.67, **Supplementary Figure 2A**). In addition, when we stratified according to the presence or absence of AF, there was no significant difference in the cumulative incidence of primary outcomes between the groups (log-rank P=0.55, **Supplementary Figure 2B**).

Discussion

The main finding of this study was that isolated moderate to severe TR was independently associated with outcome in patients with preserved LVEF and no left-sided valvular disease.

Very limited data on the association between isolated TR and outcome is currently available.[17] In addition, these data are largely derived from the cohorts of patients who underwent the tricuspid valve surgery.[18–22] There are a few reports on the natural history of isolated TR.[4,5] Topilsky et al reported that isolated TR (functional TR with no left-sided valvular disease, no decreased LVEF, and no pulmonary hypertension) significantly affected survival.[4] Lee et al reported a 26% 5-year mortality rate in isolated functional TR patients who did not undergo tricuspid valve surgery.[5] Bar et al reported that isolated TR is independently associated with outcome in patients with preserved EF and pulmonary hypertension.[6] The present results are consistent with these studies. In contrast, TR after aortic or mitral valve procedures and following transcatheter aortic valve replacement did not influence clinical outcome after adjustment for comorbidity and RV dysfunction.[23,24] This implies that in the context of right heart failure following extensive left heart disease, TR is a surrogate marker for the other heart diseases.

Before balancing for clinical backgrounds by PS, there was a significant difference in echocardiography parameters between the moderate to severe TR group and the no moderate to severe TR group. This suggests that the mechanisms underlying isolated TR may consist of 2 components: (1) TR with no left-sided valvular disease, no decreased LVEF, and no pulmonary hypertension but with or without diastolic dysfunction (e.g., TR due to AF); and (2) TR with postcapillary pulmonary hypertension due to elevated LV end-diastolic pressure without systolic dysfunction.[6,17] Therefore, these components were not be clearly separable based on the presence of diastolic dysfunction. AF, coincidentally with diastolic dysfunction or not, may cause structural right heart change through electrical remodeling.[25] TR with postcapillary pulmonary hypertension due to diastolic dysfunction and elevated LV end-diastolic pressure was the dominant form in the present study. Thus, in the present study, a substantial proportion of patients had isolated secondary (functional) TR. In this clinical context, isolated TR is independently associated with outcome, and there were no differences in outcome when stratified by the presence or absence of pulmonary hypertension and AF. We did not balance the 2 groups regarding pulmonary artery pressure hypertension; therefore, the present results indicated an association between TR and outcome, and did not suggest a potential benefit of TR-focused therapy without treatment of high pulmonary artery pressure. The indications and optimal timing for TR-focused intervention may be different between isolated TR and TR with LV or RV dysfunction. A possible role for TR-focused intervention should be confirmed in a randomized controlled study involving different clinical contexts.

Study Limitations

This study had several limitations. First, ECG and TTE were ordered at the discretion of the treating physician, with no standardized indications.[7] Second, patient data were extracted from electronic medical records, which resulted in a low follow-up rate, especially at 3 years.[8–10] In addition, a single-center retrospective study performed in Japan might result in small TR sample size. Therefore, a selection bias may exist in the present study. Third, information regarding the symptoms was not included. Thus, we had no data on the proportion of heart failure with preserved EF. Fourth, the number of patients with isolated TR was too small to draw solid conclusion from the subgroup analysis. Fifth, we did not collect data regarding drugs and biomarkers (especially drugs for heart failure), or brain natriuretic peptide levels. Finally, we did not collect quantitative data on RV dysfunction such as tricuspid annular plane systolic excursion.

Conclusions

Moderate to severe isolated TR is associated with poor clinical outcome in patients with preserved LVEF and no left-sided valvular disease.

Disclosures

The authors declare no conflicts of interest.

Author Contributions

Y.S. and T.K. conceived the design, performed statistical analysis, and wrote the manuscript. Y.S., T.K., M.S., Y.M., Y.Y., Y.H., E.N., T.H. and M.I. collected the data and made critical revisions. All authors read and approved the final manuscript.

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Supplementary Files

Please find supplementary file(s);
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