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
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.\textsuperscript{11,12} An integrative, semiquantitative approach as recommended by the American Society of Echocardiography\textsuperscript{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, tricuspid 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14} We defined high RWT as >0.42. High LVMI was defined as >115 g/m\textsuperscript{2} for male patients and >95 g/m\textsuperscript{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 \(\geq 7\) cm/s and low e’ as <7 cm/s, and normal E/e’ as \(\leq 14\) and high E/e’ as >14 according to the American Society of Echocardiography guidelines.\textsuperscript{15} High LAVI was defined as >34 mL/m\textsuperscript{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.\textsuperscript{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.\textsuperscript{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
Isolated TR and Outcome

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 characteristics: age, LVEF (as continuous variables), and sex, and the history of diabetes mellitus, hypertension, dyslipidemia, 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.

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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 relative to that 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 ≥60mmHg, 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.3–7 In addition, these data are largely derived from the cohorts of patients who underwent the tricuspid valve surgery.6–8 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.22–24 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.4,7 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., 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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