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Original Research

Late Progression of Tricuspid Regurgitation After Transcatheter Aortic Valve Replacement

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ABSTRACT

Background: Few studies have investigated the progression of baseline mild or less tricuspid regurgitation (TR) after transcatheter aortic valve replacement (TAVR). The aim of this study was to investigate the prevalence and predictors of late progression of baseline mild or less TR and the impact of late progression on outcomes after TAVR.

Methods: We reviewed 1615 patients who had baseline mild or less TR and 1-year echocardiographic follow-up registered in the Optimized Catheter Valvular Intervention–Transcatheter Aortic Valve Implantation registry. We compared outcomes including 2-year all-cause mortality, cardiac mortality, and heart failure hospitalization between groups with and without progression of TR on 1-year transthoracic echocardiography (TTE) and investigated predictors of progression of TR after TAVR.

Results: On 1-year TTE, TR worsened to a moderate or severe grade in 87 patients (5.4%). The group with TR progression had higher 2-year all-cause mortality, cardiac mortality, and heart failure hospitalization than the group without TR progression. The multivariable analysis showed that TR progression was significantly associated with all-cause mortality (hazard ratio, 4.08; 95% CI, 1.92-8.67; $P < .001$) and heart failure hospitalization (hazard ratio, 2.85; 95% CI, 1.64-4.93; $P < .001$). Independent predictors of TR progression included atrial fibrillation, transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE, and systolic pulmonary artery pressure ≥40 mm Hg.

Conclusions: TR progression from mild or less to moderate or severe after TAVR was more likely observed in patients with low transaortic gradients, atrial fibrillation, or pulmonary hypertension. TR progression after TAVR was associated with increased all-cause mortality and heart failure hospitalization.

Abbreviations: AS, aortic stenosis; LV, left ventricle; MR, mitral regurgitation; PG, pressure gradient; RV, right ventricle; SAVR, surgical aortic valve replacement; sPAP, systolic pulmonary artery pressure; TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Keywords: Transcatheter aortic valve replacement; tricuspid regurgitation; late progression.

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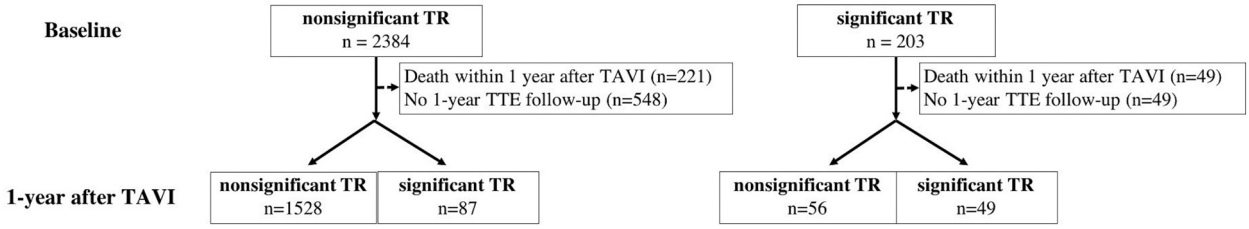


Figure 1. Study flowchart. TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Introduction

In patients undergoing transcatheter aortic valve replacement (TAVR) for severe aortic stenosis (AS), the reported prevalence of significant (moderate or severe) tricuspid regurgitation (TR) ranges from 11% to 27%.[1–4] Significant TR is reported to be associated with high all-cause mortality after TAVR in the meta-analysis.[5] Lack of improvement in TR following TAVR also was reported as a predictor of mortality.[1] On the other hand, prognosis of patients with nonsignificant TR after TAVR has been poorly defined. Since remaining significant TR is known to be associated with poor outcomes after TAVR, progression of TR from a nonsignificant to significant grade could be associated with poor outcomes too. Knowing which TAVR patients are likely to develop TR progression should be helpful to establish optimal heart failure management after TAVR and to determine the timing of tricuspid valve interventions in those patients. In this study, we aimed to investigate the prevalence, predictors of TR progression after TAVR, and the impact of TR progression on all-cause mortality and heart failure hospitalization.

Method

Study population and design

The OCEAN-TAVI registry is an ongoing, prospective, multicenter TAVR registry of high-risk or inoperable severe AS patients affiliated with 14 institutions in Japan. This registry is registered with the University Hospital Medical Information Network (UMIN000020423). The inclusion criteria of this registry were previously reported.[6,7] All patients were treated with TAVR based on the clinical consensus of a heart team comprised of cardiac surgeons, interventional cardiologists, and anesthesiologists. Between October 2013 and May 2017, 2588 TAVR patients were registered in the OCEAN-TAVI registry. Among those, 203 patients had baseline significant TR (Figure 1) and no patient had received previous tricuspid valve replacement or tricuspid valvuloplasty. In this study, we focused on patients with nonsignificant TR at the time of TAVR. After excluding 221 patients who died within 1 year after TAVR and 548 patients who had no 1-year transthoracic echocardiography (TTE) follow-up, we reviewed 1615 TAVR patients and divided them into 2 groups: patients with TR progression on 1-year TTE (group A) and patients without TR progression to a significant grade (group B) (Figure 1). We obtained clinical data prospectively including patients' characteristics, operative risk, echocardiographic data, and 2-year outcomes in the OCEAN-TAVI registry database. The follow-up data were collected by each hospital team in either of the following ways: interview at planned hospital visit, telephone interview, and questionnaire. TTE was performed before TAVR, before discharge after TAVR, and at 1 year after TAVR. The conventional parameters were measured according to current guidelines.[8–10] TR severity was determined by an integrative, semiquantitative approach as recommended by the European Association of Cardiovascular Imaging, including assessment of color-flow area of the TR jet, vena contracta width, tricuspid valve morphology, hepatic venous flow pattern at the parasternal RV inflow, parasternal short axis, apical 4-chamber view, and subcostal views. Mild TR was defined as a small central jet, moderate TR as an intermediate jet, and severe TR as a very large central jet or eccentric wall-impinging jet, or vena contracta width >7 mm, or in the presence of systolic flow reversal in the hepatic veins.[10] We defined "significant" TR as moderate or severe TR and "nonsignificant" TR as mild or less TR. TR progression was defined as a TR increase from a nonsignificant to significant grade. The institutional review board at each institution approved this study protocol. A written informed consent was obtained from all patients before TAVR procedure.

Procedures

The details of TAVR procedure have been previously described.[11,12] In this study, patients were treated with balloon-expandable Edwards Sapien XT/Sapien S3 prosthesis (Edwards Lifesciences) or Medtronic CoreValve/Evolut R prosthesis (Medtronic) via transfemoral, transiliac, transapical, trans-subclavian, and transaortic approach. The prosthesis type, size, and approach site were determined based on the findings from procedural echocardiography and multidetector computed tomography. The procedural outcomes and complications were defined based on the VARC-2 criteria.

Clinical endpoints

The primary outcomes were all-cause mortality, cardiac mortality, and heart failure hospitalization at 2 years after TAVR procedure. We compared those outcomes between 2 groups and evaluated the association of TR progression with 2-year mortalities and heart failure hospitalization using multivariable analyses. We also identified independent predictors of TR progression at 1 year after TAVR.

Statistical analysis

Continuous variables were reported as mean and SD or medians with interquartile range and compared using the *t* test or Wilcoxon rank-sum test based on distributions. Categorical variables were described as frequency and compared using the χ^2 test or Fisher exact test when appropriate. Two-year event rates were presented by Kaplan-Meier estimate in time-to-first-event analysis and compared with the log-rank test. The Cox regression analysis was used to identify an independent predictor associated with 2-year outcomes. We included the following variables as potential confounders in the model: baseline age, sex, body mass index (BMI) $\geq$25 kg/m^2, chronic kidney disease, atrial fibrillation, transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE, chronic obstructive pulmonary disease, left ventricular ejection fraction (LVEF) < 50%, moderate or severe mitral regurgitation (MR), New York Heart Association class 3 or 4, Society of Thoracic Surgeons Predicted Risk of Morality, systolic pulmonary artery pressure $\geq$40 mm Hg, left ventricle (LV) stroke volume, TR progression at 1 year after TAVR, moderate or severe aortic regurgitation on predischarge TTE, and pacemaker

implantation before TAVR or within 1 year after TAVR. Those variables were selected based on clinical significance referred to previous studies.[13,14] The results of the multivariable Cox regression analysis were expressed as hazard ratios (HR) for the comparison of risk with 95% confidence interval (CI). The logistic multivariable analysis was used to identify predictors of late TR progression. We included the following variables in the model and calculated odds ratios (OR) and 95% CIs: baseline age, LVEF <50%, sex, atrial fibrillation, BMI ≥25 kg/m^2, transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE, systolic pulmonary artery pressure ≥40 mm Hg, LV stroke volume, moderate or severe aortic regurgitation on predischarge TTE, moderate or severe MR, chronic obstructive pulmonary disease, and pacemaker implantation before TAVR or within 1 year after TAVR. All *P* values were 2 sided, and values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[15] which is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Result

Prevalence of TR progression after TAVR

Among 1615 patients, TR remained nonsignificant in 1528 patients and progressed to a significant level in 87 patients on 1-year TTE. The prevalence of TR progression after TAVR among patients without significant baseline TR was 5.4%.

Patient background and predictors of TR progression

Patients' clinical background is shown in Table 1. Group A had older age, higher BMI, higher body surface area, more frequent chronic kidney disease, atrial fibrillation, and higher operative risk scores than group B. Echocardiographic characteristics before TAVR are shown in Table 2.

Table 1. Baseline clinical characteristics of study populations

	Group A TR progression (+) $n = 87$	Group B TR progression (−) $n = 1528$	*P*
Age, years	85.6 ± 4.4	84.3 ± 5.1	.027
Male	22 (25.3%)	471 (30.8%)	.34
BMI, kg/m^2	21.5 ± 3.5	22.4 ± 3.5	.012
BSA, m^2	1.4 ± 0.16	1.44 ± 0.17	.017
CSHA frailty index	3.8 ± 1.1	3.7 ± 1.2	.83
NYHA class 3 or 4	45 (51.7%)	705 (46.1%)	.32
Current smoking	1 (1.1%)	30 (2%)	1
Dyslipidemia	38 (43.7%)	705 (46.1%)	.74
Diabetes mellitus	18 (20.7%)	314 (20.5%)	1
Hypertension	70 (80.5%)	1192 (78%)	.69
CKD	66 (75.9%)	1002 (65.6%)	.049
Atrial fibrillation	34 (39.1%)	254 (16.6%)	<.001
Prior PMI	5 (5.7%)	88 (5.8%)	1
PAD	6 (6.9%)	187 (12.2%)	.17
Previous myocardial infarction	5 (5.7%)	98 (6.4%)	1
Prior CABG	4 (4.6%)	94 (6.2%)	.82
Prior other cardiac surgery	1 (1.1%)	13 (0.9%)	.54
Previous stroke	4 (4.6%)	134 (8.8%)	.24
COPD	9 (10.3%)	205 (13.4%)	.52
EuroSCORE II, %	3.78 (2.7-6)	3.4 (2.1-5.2)	.037
STS-PROM, %	7.2 (4.8-11.1)	6.0 (4.3-8.6)	.014

Values are shown as *n* (%), mean ± SD, or median (interquartile range).
BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CSHA, Canadian Study for Health and Aging; EuroSCORE II, European Systems for Cardiac Risk Evaluation II; NYHA, New York Heart Association; PAD, peripheral artery disease; PMI, pacemaker implantation; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Morality; TR, tricuspid regurgitation.

Table 2. Echocardiographic characteristics before TAVR

	Group A TR progression (+) $n = 87$	Group B TR progression (−) $n = 1528$	*P*
LVEF, %	58.4 ± 13.2	59.7 ± 12.2	.35
AVA, cm^2	0.62 ± 0.19	0.64 ± 0.17	.27
LVEDV, mL	78.1 ± 31.6	86.8 ± 33.4	.044
LVESV, mL	26.5 (19.4-46.5)	30.1 (21.3-48.5)	.18
LAD, mm	44.4 ± 8.7	41.6 ± 6.6	<.001
Left ventricle stroke volume, mL	59.3 ± 18.8	65.5 ± 19.4	.005
Left ventricle stroke volume index, mL/m^2	41.4 ± 14.2	44.6 ± 14.5	.054
Transaortic mean PG, mm Hg	47 ± 16.4	51.5 ± 17.6	.02
Transaortic peak PG, mm Hg	80.5 ± 27.23	87.6 ± 28.3	.023
Moderate/severe AR	8 (9.2%)	132 (8.6%)	.84
Moderate/severe MR	17 (19.5%)	117 (7.7%)	<.001
sPAP, mm Hg	36.9 ± 10	31.4 ± 9.9	<.001

Values are shown as *n* (%), mean ± SD, or median (interquartile range).
AR, aortic regurgitation; AVA, aortic valve area; LAD, left atrial dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PG, pressure gradient; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

Group A had more frequent moderate or severe MR and higher systolic pulmonary artery pressure. Procedure characteristics are shown in Table 3. The access route, prosthesis size, and valve type did not differ between 2 groups.

The multivariable analysis showed that atrial fibrillation (OR, 2.18; 95% CI, 1.28-3.72; $P = .0042$), transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE (OR, 1.92; 95% CI, 1.14-3.22; $P = .014$), and systolic pulmonary artery pressure ≥40 mm Hg (OR, 2.24; 95% CI, 1.29-3.9; $P = .004$) were independent predictors of TR progression after TAVR (Table 4).

Table 3. Procedural characteristics and procedural outcomes

	Group A TR progression (+) $n = 87$	Group B TR progression (−) $n = 1528$	*P*
Approach			.54
Transfemoral	79 (90.8%)	1268 (83%)	
Transapical	8 (9.2%)	216 (14.1%)	
Direct aortic	0	5 (0.3%)	
Transiliac	0	24 (1.6%)	
Trans-subclavian	0	15 (1%)	
Valve size			.62
20 mm	4 (4.6%)	56 (3.7%)	
23 mm	47 (54%)	808 (52.9%)	
26 mm	26 (29.9%)	529 (34.6%)	
29 mm	10 (11.5%)	135 (8.8%)	
Valve type			.27
Sapien XT	46 (52.9%)	877 (57.4%)	
Sapien S3	28 (32.2%)	479 (31.3%)	
CoreValve	5 (5.7%)	102 (6.7%)	
Evolut R	8 (9.2%)	70 (4.6%)	
Predischarge TTE			
LVEF, %	59.2 ± 11.3	59.8 ± 10.5	.66
Effective orifice area, cm^2	1.67 ± 0.48	1.68 ± 0.46	.73
Transaortic mean PG, mm Hg	9.4 ± 3.9	11 ± 4.7	.0017
Moderate/severe AR	1 (1.1%)	23 (1.5%)	.657
Clinical in-hospital outcomes			
Periprocedural MI	0 (0%)	10 (0.7%)	1
Stroke	1 (1.1%)	23 (1.5%)	1
Pacemaker implantation	10 (11.5%)	112 (7.3%)	.15
Life-threatening/major bleeding	6 (6.9%)	177 (11.6%)	.22
Major vascular complication	0 (0%)	55 (3.6%)	.07

AR, aortic regurgitation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PG, pressure gradient; TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Table 4. Multivariable predictors of TR progression

	OR	95% CI	*P*
Age	1.03	0.98-1.09	.20
Left ventricular ejection fraction <50%	1.00	0.54-1.83	.99
Male	1.06	0.6-1.86	.85
Body mass index ≥25 kg/m^2	0.80	0.42-1.52	.50
Atrial fibrillation	2.18	1.28-3.72	.0042
Transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE	1.92	1.14-3.22	.014
sPAP ≥40 mm Hg	2.24	1.29-3.9	.004
Left ventricle stroke volume, mL	0.99	0.98-1.01	.36
AR moderate or severe on predischarge TTE	0.77	0.09-6.37	.81
MR moderate-severe	1.15	0.52-2.55	.74
Chronic obstructive pulmonary disease	0.63	0.27-1.45	.28
Pacemaker implantation before TAVR or within 1 year after TAVR	1.34	0.71-2.56	.37

AR, aortic regurgitation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PG, pressure gradient; TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Primary outcomes

Primary outcomes are shown in Table 5. Group A had higher 2-year all-cause mortality rate (10.3% vs 3.9%; $P < .001$), cardiac mortality (3.4% vs 1.3%; $P = .041$), and rate of heart failure hospitalization (11.5% vs 3.4%; $P < .001$) (Central Illustration). The multivariable analysis showed that 1-year TR progression was significantly associated with increased all-cause mortality (HR, 4.08; 95% CI, 1.92-8.67; $P < .001$) and higher incidence of heart failure hospitalization (HR, 2.85; 95% CI, 1.64-4.93; $P < .001$) (Tables 6 and 7). In addition, the predictor of all-cause mortality is male sex (HR, 2.7; 95% CI, 1.52-4.8; $P < .001$), and the predictors of heart failure hospitalization are male sex (HR, 1.74; 95% CI, 1.12-2.71; $P = .014$), transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE (HR, 1.74; 95% CI, 1.13-2.66; $P = .011$), and moderate or severe MR (HR, 1.78; 95% CI, 1.02-3.12; $P = .044$).

Discussion

The findings of the present study were as follows: (a) TR progression at 1 year was observed in 5.4% of TAVR patients without baseline significant TR, (b) atrial fibrillation, transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE, and systolic pulmonary artery pressure ≥40 mm Hg were significant predictors of TR progression at 1 year after TAVR, (c) patients with TR progression at 1 year after TAVR had higher 2-year mortality, cardiac mortality, and heart failure hospitalization than those without TR progression, and (d) TR progression at 1 year after TAVR was significantly associated with higher all-cause mortality and heart failure hospitalization after adjusting confounding factors.

In PARTNER II trial cohort B which consisted of inoperable patients, among 1-year survivors with nonsignificant TR at baseline, 19% had progression to significant TR.[3] In our study, fewer patients (5.4%) had progression to significant TR. When comparing PARTNER II trial cohort B to the present study, there were differences in baseline atrial fibrillation (30% vs 17.8%), chronic lung disease (17% vs 13.3%), and significant MR (27% vs 8.3%), which could have caused the differences in the prevalence of TR progression after TAVR.

The prevalence of TR progression after left-sided valve surgery has been reported as 7.7%-26.9%.[16–19] Song et al[16] retrospectively reviewed more than 600 patients after left heart valve procedure and showed that late significant TR was associated with worse outcome, defined as a combination of cardiovascular death, need for redo surgery, and heart failure hospitalization. Matsuyama et al[19] reported predictors of late significant TR, and multivariable analysis identified preoperative mild TR (OR, 3.9; 95% CI, 1.5-9.7; $P = .004$), atrial fibrillation (OR, 9.2; 95% CI, 1.1-74.0; $P = .03$), and huge left atrium (OR, 2.8; 95% CI, 1.1-7.2; $P = .03$) as statistically significant predictors for late TR after mitral valve

Table 5. Primary outcomes at 2 years

	Group A TR progression (+)	Group B TR progression (−)	*P*
All-cause death	9 (10.3%)	60 (3.9%)	<.001
Cardiac death	3 (3.4%)	20 (1.3%)	.041
Heart failure hospitalization	10 (11.5%)	52 (3.4%)	<.001

Number of events (event rates) were presented by Kaplan-Meier estimate in time-to-first-event analysis and compared with the log-rank test.

Table 6. Multivariable predictors of all-cause mortality

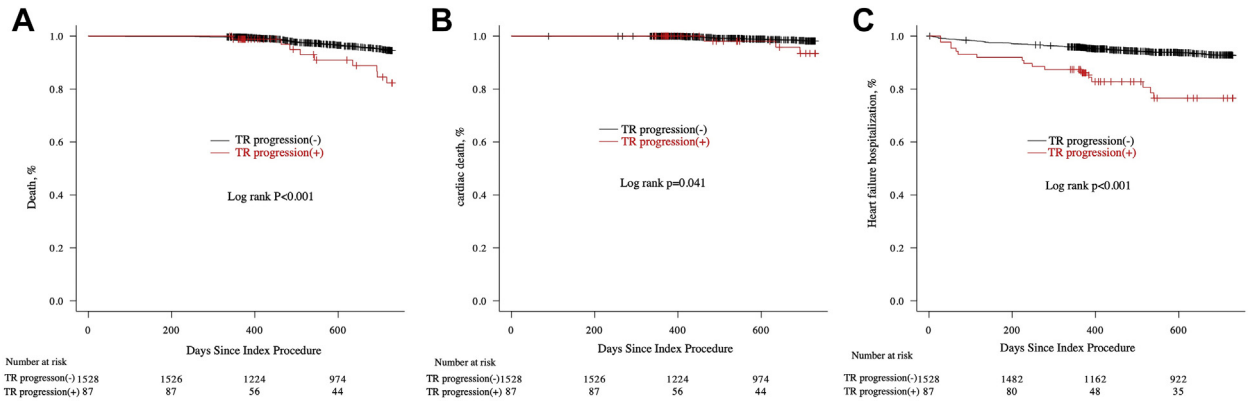
	HR	95% CI	*P*
Atrial fibrillation	0.55	0.25-1.24	.15
Male	2.70	1.52-4.80	<.001
Age	1.02	0.96-1.08	.54
Body mass index ≥25, kg/m^2	0.74	0.34-1.59	.43
Transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE	0.67	0.35-1.28	.23
Chronic obstructive pulmonary disease	1.28	0.65-2.54	.47
Chronic kidney disease	0.80	0.44-1.44	.45
Left ventricular ejection fraction <50%	1.82	0.98-3.37	.057
MR moderate-severe	1.43	0.62-3.29	.40
NYHA class 3 or 4	1.50	0.84-2.67	.17
STS-PROM, %	1.01	0.97-1.05	.52
sPAP ≥40 mm Hg	0.99	0.49-1.99	.98
Left ventricle stroke volume, mL	0.99	0.97-1.00	.059
TR progression at 1 year	4.08	1.92-8.67	<.001
AR moderate-severe on predischarge TTE	1.22	0.16-9.14	.85
Pacemaker implantation before TAVR or within 1 year after TAVR	1.04	0.50-2.18	.91

AR, aortic regurgitation; CI, confidence interval; HR, hazard ratio; MR, mitral regurgitation; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Morality; TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Table 7. Multivariable predictors of heart failure hospitalization at 2 years

	HR	95% CI	*P*
Atrial fibrillation	1.15	0.71-1.84	.58
Male	1.74	1.12-2.71	.014
Age	1.02	0.97-1.06	.49
Body mass index ≥25 kg/m^2	0.89	0.53-1.48	.65
Transaortic mean pressure gradient <40 mm Hg on pre-TAVR TTE	1.74	1.13-2.66	.011
Chronic obstructive pulmonary disease	0.83	0.46-1.49	.53
Chronic kidney disease	1.52	0.91-2.54	.11
Left ventricular ejection fraction <50%	1.25	0.78-2.02	.35
MR moderate-severe	1.78	1.02-3.12	.044
NYHA class 3 or 4	1.26	0.82-1.93	.30
STS-PROM, %	1.01	0.99-1.04	.23
sPAP ≥40 mm Hg	2.04	1.31-3.19	.0017
Left ventricle stroke volume, mL	1.00	0.99-1.01	.83
TR progression at 1 year	2.85	1.64-4.93	<.001
AR moderate-severe on predischarge TTE	1.67	0.51-5.48	.40
Pacemaker implantation before TAVR or within 1 year after TAVR	1.39	0.83-2.33	.20

AR, aortic regurgitation; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PG, pressure gradient; sPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Morality; TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.



Central Illustration. Time-to-event curve for the 2-year outcomes. All-cause mortality, cardiac mortality, and rate of heart failure hospitalization were higher in the TR progression group. (**A**) All-cause mortality, (**B**) cardiac mortality, and (**C**) heart failure hospitalization. TR, tricuspid regurgitation.

surgery. Kwak et al[18] also reported atrial fibrillation was the only predictor for late TR in multivariable analysis (OR, 5.37; 95% CI, 2.71-10.65; $P < .001$), and Fuster et al[17] reported that the maze operation showed a protective effect in development of late TR after mitral valve replacement, with an incidence of 6.7% of late, significant TR in comparison to 13.2% in those patients without maze ($P = .04$).

The most common mechanisms of TR are tricuspid annular dilatation and leaflet tethering in the setting of right ventricular remodeling due to pressure or volume overload. It has been shown that the degree of diffuse interstitial fibrosis remained unchanged despite the improvement of LV hypertrophy after surgical aortic valve replacement (SAVR) in some AS patients.[20] Persistent LV interstitial fibrosis leads to remaining diastolic dysfunction, elevated LV end-diastolic pressures, and postcapillary pulmonary hypertension. Persistent pulmonary hypertension leads to increased right ventricle (RV) size, RV dysfunction, and worsening TR.[4] The relief of the aortic valve gradient increases stroke volume, which increases systemic venous return and RV volume load. Especially in patients with poor right heart function, the RV is unable to accommodate the additional volume, and then TR worsens.[10] Atrial fibrillation induces atrial remodeling and tricuspid annular dilation which, in turn, develops late TR; also, persistent pulmonary hypertension causes RV enlargement and RV dysfunction, which induces leaflet tethering and worsening TR. These mechanisms could explain our results.

RV function is another important factor of TR progression. Whether RV can manage increased venous return after TAVR or SAVR or not depends on RV function. Kammerlander et al[4] reported that preserved RV function is associated with lower mortality after left-sided valve surgery (HR, 0.945; 95% CI, 0.922-0.968; $P < .001$) and that TR is not associated with morality. Schwartz et al[1] also reported the same findings in AS patients undergoing TAVR. They also have shown that tricuspid annular plane systolic excursion was the best parameter to assess RV function in patients after TAVR.

On the other hand, Lindman et al[3] reported that severe TR (HR, 3.2; 95% CI, 1.5-6.82; $P = .003$) and RV dilation (HR, 2.20; 95% CI, 1.24-3.9; $P = .007$) were associated with increased mortality, whereas poor RV dysfunction (HR, 1.62; 95% CI, 0.87-3.01; $P = .13$) was not.

Our study showed that low-gradient severe AS is a predictor of TR progression after TAVR. Herrmann et al reported that low-gradient severe AS patients frequently have extensive interstitial myocardial fibrosis regardless of their LVEF and that those patients also demonstrate a decreased LV stroke volume.[21] These findings could affect RV function and TR after TAVR. Galli et al investigated the prevalence of RV dysfunction in severe AS patients and showed that low-flow low-gradient AS patients more frequently had RV dysfunction than other patients with normal-gradient or normal-flow low-gradient AS (62% vs 18%).[22]

Several other studies have shown significant negative impact of TR on outcomes in various patient groups. Significant TR has been identified as a predictor of mortality in 5223 consecutive patients undergoing echocardiography[23] and in patients with mitral valve disease.[24–26] In patients undergoing TAVR, 11%-27% had significant TR at baseline and baseline significant TR was associated with 1-year mortality in univariate analysis.[1–3] Lindman et al[3] have shown that severe TR was associated with a 3-fold increase in the hazard of 1-year mortality by the multivariable analysis.

However, little is known about the impact of change in TR on clinical outcomes after TAVR. Schwartz et al reported in subgroup analysis that in 41 patients with significant TR at baseline, 24 patients improved to nonsignificant TR and 17 patients remained with significant TR. In their study, improvement in TR was associated with reduced mortality (HR, 0.31; 95% CI, 0.1-0.86; $P = .02$) and the factors associated with lack of improvement in TR after TAVR were systolic pulmonary pressure ($P = .05$), tricuspid annular diameter ($P = .01$), and atrial fibrillation ($P = .05$).[1] They have shown that the absence of TR regression after TAVR is associated with a poor outcome, which is consistent with our finding that TR progression after TAVR is associated with a poor outcome.

Our findings suggest potential clinical benefits of careful monitoring or interventions for TR during or after aortic valve interventions (eg, concomitant tricuspid valve annuloplasty with SAVR or transcatheter tricuspid valve repair after TAVR or SAVR) in patients with severe AS requiring interventions who have atrial fibrillation, pulmonary artery hypertension, and/or low aortic valve gradient.

Limitation

There are several limitations of our study. First, this study is limited by its retrospective nature, and there were potential unadjusted biases. Second, despite TR severity was evaluated according to current guidelines, collected data were based on echocardiographic measurement at individual institutions and might have less uniformity than measurement at a single core laboratory. Third, a significant number of patients were excluded from this study due to the lack of follow-up TTE, which might have affected our results. However, the sample size of this study is still large enough to analyze. Fourth, after 2588 patients in this study were registered, newer valves such as the Sapien 3 Ultra and the CoreValve Evolut PRO/PRO+ were developed. These contemporary valves might not apply to the results of this study. Lastly, detailed RV data such as RV size, RV contractility, and tricuspid annulus size were not assessed due to the lack of data. Further investigation is necessary regarding the relationship between the occurrence of late TR and RV dysfunction or tricuspid annulus dilatation.

Conclusion

One-year TR progression from nonsignificant to significant after TAVR is associated with high 2-year all-cause mortality and heart failure hospitalization. Baseline atrial fibrillation, low transaortic gradients, and pulmonary hypertension are predictors of TR progression after TAVR.

Declaration of competing interest

Dr Yamamoto, Dr Tada, Dr Naganuma, Dr Shirai, Dr Mizutani, Dr Tabata, Dr Ueno, and Dr Watanabe are clinical proctors for Edwards Lifesciences and Medtronic. Dr Takagi and Dr Hayashida are clinical proctors of Edwards Lifesciences. The remaining authors have nothing to disclose.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and /or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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