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ORIGINAL RESEARCH

Long-Term Clinical Outcomes in Patients With Severe Tricuspid Regurgitation

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BACKGROUND: The natural history and optimal interventional timing in patients with isolated severe tricuspid regurgitation (TR) have not been well studied. This study aimed to investigate long-term clinical outcomes and risk factors associated with poor prognosis in patients with isolated severe TR.

METHODS AND RESULTS: Consecutive transthoracic echocardiographic examinations in 2877 patients with isolated severe TR were retrospectively reviewed. Patients with significant left-sided valve disease or repeated examinations were excluded. Primary outcome was defined as a composite of all-cause death and hospitalization for heart failure. Among the 613 enrolled patients (mean age, 74±13 years; men, 38%), 141 died, and 62 were hospitalized for heart failure during the median follow-up period of 26.5 (interquartile range, 6.0–57.9) months. The 5-year event-free rate was 60.1%. TR pressure gradient (adjusted hazard ratio [HR], 1.03 [95% CI, 1.01–1.04]), blood urea nitrogen (adjusted HR, 1.02 [95% CI, 1.01–1.04]), left atrial volume index (adjusted HR, 1.01 [95% CI, 1.002–1.02]), and serum albumin (adjusted HR, 0.56 [95% CI, 0.36–0.95]) were identified as independent predictors of adverse events. A risk model based on the 4 clinical factors that included pulmonary hypertension (TR pressure gradient >40 mm Hg), elevated blood urea nitrogen levels (>25 mg/dL), decreased albumin levels (<3.7 g/dL), and left atrial enlargement (left atrial volume index <34 mL/m^2) revealed a graded increase in the risk of adverse events (P<0.001).

CONCLUSIONS: The prognosis of isolated severe TR is not always favorable. Careful attention should be paid to patients with concomitant risk factors, such as pulmonary hypertension, elevated blood urea nitrogen levels, decreased albumin levels, and left atrial enlargement.

Key Words: heart failure ■ prognosis ■ surgery ■ tricuspid regurgitation ■ valvular heart disease

Tricuspid regurgitation (TR) is a common echocardiographic finding, and it is encountered in 70% to 90% of the general population. TR has been believed to be a benign disease as it is often asymptomatic and can be managed conservatively with treatments such as diuretic therapy.[1] However, it can sometimes cause right-sided heart failure and require surgical or catheter intervention.[2] Recent studies demonstrated that increased TR severity was associated with higher mortality.[3,4] Although surgical mortality can be adversely affected by delayed surgical intervention,[2,5] the optimal timing of intervention for TR remains controversial. A recent study also reported that the prognosis of surgically treated moderate or greater TR did not differ significantly from that treated using medical therapy.[5] Thus, the natural history and risk factors associated with poor outcomes in isolated severe TR remain understudied. Therefore, we aimed to determine the long-term clinical outcomes and risk factors associated with poor prognosis in patients with isolated severe TR to determine the optimal timing for intervention.

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CLINICAL PERSPECTIVE

What Is New?

- Patients with severe tricuspid regurgitation may experience adverse events in the long-term.
- A risk model based on pulmonary hypertension, renal and/or liver dysfunction, and left atrial enlargement showed a graded increase in the risk of future adverse events.

What Are the Clinical Implications?

- Intervention might be needed in patients with isolated severe tricuspid regurgitation with concomitant risk factors suspecting multiorgan damages.
- Additional studies are required to evaluate the influence of the interventions on clinical outcomes in patients with severe tricuspid regurgitation with concomitant risk factors.

Nonstandard Abbreviations and Acronyms

LAVi	left atrial volume index
TR	tricuspid regurgitation
TRPG	tricuspid regurgitation pressure gradient

METHODS

Study Design and Setting

The data that support the findings of this study are available from the corresponding author on reasonable request. This is a retrospective study of consecutive echocardiographic examinations conducted between August 2011 and August 2019 at the echocardiography laboratory of Kobe City Medical Center General Hospital (Kobe, Japan). A total of 2877 consecutive echocardiographic examinations reporting severe TR were retrospectively reviewed. Patients were excluded if they presented with significant left-sided valve disease (n=1568) or underwent second and subsequent examinations during the study period (n=696). Finally, 613 patients were included (Figure S1). Isolated severe TR was defined as severe TR without significant left-sided valve diseases (greater than mild). Because there is no consensus on the definition of isolated TR and it varied among previous publications, we included patients with severe TR without significant left-sided valve disease greater than mild in the main analysis. As a sensitivity analysis, we excluded those with primary TR, surgical history of left-sided valve disease, left ventricular dysfunction, and pulmonary hypertension. The primary outcome measure was defined as a composite of all-cause death and hospitalization for heart failure. Demographic and clinical characteristics of all patients, including age, sex, laboratory findings, history of hypertension, diabetes, dyslipidemia, coronary artery disease, chronic kidney disease, atrial fibrillation or flutter, pacemaker or implantable cardioverters-defibrillators, chronic obstructive pulmonary disease, interstitial pneumonia, active cancer, and oral administration of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β blocker, mineralocorticoid receptor antagonists, and diuretics, were collected from the electronic health records. Symptomatic was defined as the presence of dyspnea on exertion, oxygen administration, edema, or prescription of diuretics. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min at stability[6]; chronic obstructive pulmonary disease was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease spirometry criteria and history of smoking.[7] Interstitial pneumonia was defined as a disease with no reversible cause based on clinical signs and imaging findings, respiratory function test findings, and classification in international guidelines.[8] Patients with active cancer were defined as those diagnosed with cancer within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within 6 months; or hematological cancer that is not in complete remission.[9]

The study was approved by the Institutional Review Board of Kobe City Medical Center General Hospital. The requirement for obtaining patient informed consent was waived because of the retrospective nature of the study.

Echocardiography and Evaluation of TR Severity

Echocardiography was performed in a standard manner with the following commercially available echocardiographic machines: IE 33, EPIQ 7, EPIQ Elite (Philips Healthcare, Eindhoven, North Brabant, the Netherlands), Artida (Canon Medical Systems, Otawara, Tochigi, Japan), and ACUSON SC 2000 (SIEMENS Healthineers, Erlangen, Bavaria, Germany). TR severity was determined using the integrative, qualitative, and semiquantitative approaches, as recommended by the American Society of Echocardiography.[10] TR severity was assessed according to the width of the vena contracta and jet area of regurgitation with systolic flow reversal in the hepatic veins. Because quantitative assessments were not available in this retrospective study, blinded TR regrading was performed by 2 experienced cardiologists (N.M and M.S.) in 30 randomly selected cases to ensure the reliability of the severity diagnosis. No patients were diagnosed with

TR of moderate or less severity. In cases of massive TR with laminar flow, we did not measure TR pressure gradient (TRPG) from the jet velocity because it is less reliable for the estimation of pulmonary artery pressure. All echocardiographic examinations were performed by experienced sonographers and confirmed by licensed echocardiologists (T.K and T.O.).

Statistical Analysis

Categorical variables are shown as numbers and percentages and were compared using the χ^2 test or Fisher exact test, as appropriate. Continuous variables are expressed as mean and SD or median and interquartile range. Depending on their distribution (qualitatively judged via histogram and Q-Q plot), continuous variables were compared using the Student *t* test or Wilcoxon rank-sum test, as appropriate. Two-sided $P<0.05$ was considered statistically significant. The Kaplan-Meier method was used to estimate the cumulative incidence of events, and the differences were compared using the log-rank test. A Cox proportional hazards model was used to evaluate the association between each variable and the incidence of adverse events, defined as a composite of all-cause death and hospitalization for heart failure. Clinical follow-up data were obtained from medical records or directly from patients either in person or during telephone interviews. We used the following conventional prognostic factors as the risk-adjusting variables: age, sex, body mass index, cardiovascular risk factors, pharmacologic therapy for heart failure, blood collection results, including indicators of liver and renal function, nutritional status,[11] and echocardiographic findings, such as left ventricular contractility, diastolic function, and right ventricular overload. All variables were selected a priori as they were either known predictors of the outcomes in patients with TR or because of their ability to confound the relationship. Proportional hazard assumption violations were estimated by generalized linear regression of scaled Schoenfeld residuals on time. In addition, we constructed a risk model using 4 clinical variables: pulmonary hypertension, blood urea nitrogen, albumin, and TRPG. Statistical analyses were performed using the statistical software program JMP 14.0.0 (SAS Institute Inc, Cary, NC) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The baseline characteristics of the 613 study patients are shown in Table 1. The mean age was 74±13 years, and 38% were men. The proportion of patients with a history of left-sided valve surgery was 24.3%, 282 patients (46%) had atrial fibrillation, and 58 patients (10.3%) had pacemakers or implantable cardioverters-defibrillators. Forty-four patients (7.1%) had pulmonary disease, which is listed as a possible cause of pulmonary hypertension that can lead to TR.[12] Diuretics were administered to 240 patients (45.2%). Left ventricular ejection fraction was maintained in most patients. The proportion of patients with prescription of cardioprotective drugs for heart failure with reduced left ventricular ejection fraction, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and mineralocorticoid receptor blockers, was low (≈25%). Of the patients, 266 (43.4%) were symptomatic, and median vena contracta width was 9.2 (interquartile range, 7.9–11.3) mm. Seventy-one patients were diagnosed with primary TR; pacemaker related (n=58), Ebstein disease (n=7), prolapse (n=5), and endocarditis (n=1). Outpatient echocardiographic examinations were performed in 420 patients (68.5%), whereas 193 patients (31.5%) underwent echocardiography during hospitalization. The reasons for obtaining the echocardiographic examinations were routine clinical follow-up (42%), further evaluation for symptoms suggestive of heart failure (23%), and further evaluation before noncardiac surgery or chemotherapy (19%).

Outcomes and Risk Factors for Adverse Events

During the median follow-up period of 26.5 (interquartile range, 6.0–57.9) months, 141 patients (23.3%) died, and 62 (10.2%) were hospitalized because of heart failure. Over the entire follow-up period, 180 patients (29.4%) had experienced an adverse event. A total of 19% of the patients experienced adverse events within 1 year after their study enrollment. The overall 5-year adverse event–free rate was 60.1% (Figure 1). Fifteen patients underwent tricuspid valve surgery after diagnosis, and no deaths occurred during the follow-up period. Table 2 shows the results of the univariate and multivariable analyses for predicting future adverse events. Multivariable analysis identified older age (adjusted hazard ratio [HR], 1.04 [95% CI, 1.02–1.07]; $P<0.001$); male sex (adjusted HR, 2.16 [95% CI, 1.26–3.70]; $P=0.005$); higher TRPG (adjusted HR, 1.03 [95% CI, 1.01–1.04]; $P<0.001$); blood urea nitrogen (BUN) level (adjusted HR, 1.02 [95% CI, 1.01–1.04]; $P=0.009$); left atrial volume index (LAVi) (adjusted HR, 1.01 [95% CI, 1.002–1.02]; $P=0.017$); and lower serum albumin level (adjusted HR, 0.56 [95% CI, 0.36–0.95]; $P=0.030$) as independent predictors of adverse events. Although echocardiographic examination during hospitalization was associated with poor outcomes in the univariable analyses (HR, 3.07 [95% CI, 2.27–4.14]; $P<0.001$), it was not statistically significant in the multivariable analyses (adjusted HR, 1.42 [95% CI, 0.82–2.47]; $P=0.210$).

Table 1. Characteristics, Comorbidities, Medication, and Laboratory and Echocardiography Findings at the Time of Diagnosis in the Overall Cohort

Baseline clinical and echocardiographic characteristics	All patients (n=613)	Missing values, n
Characteristics/comorbidities		
Age, y	74±13	0
Male sex	231 (37.6)	0
Body mass index, kg/m^2	20.7 (18.7–23.2)	4
Hypertension	207 (36.8)	51
Diabetes	93 (16.5)	51
Hyperlipidemia	102 (18.5)	51
Chronic kidney disease	60 (10.6)	51
Atrial fibrillation/flutter	282 (46)	0
Pacemaker/implantable cardioverters-defibrillators	58 (10.3)	51
Ischemic heart disease	72 (12.8)	51
COPD/IP	40 (7.1)	51
Surgery for left-sided valve disease	149 (24.3)	0
Active malignancy	55 (9.9)	51
Symptomatic	266 (43.4)	0
Medication at diagnosis		
ACEI/ARB	129 (24.3)	82
β-Blocker	155 (29.2)	82
MRA	127 (23.9)	82
Diuretics	240 (45.2)	82
Laboratory findings		
Total bilirubin, mg/dL	0.7 (0.5–1.0)	14
Albumin, g/dL	3.6±0.7	84
AST, IU/L	25 (20–32)	14
ALT, IU/L	17 (13–26)	14
Acetylcholinesterase, IU/L	224±78	29
BUN, mg/dL	22.4±13.7	14
Creatinine, mg/dL	0.84 (0.66–1.13)	14
Sodium, mEq/L	139±4	14
Potassium, mEq/L	4.2±0.5	14
Chloride, mEq/L	104±5	38
BNP, ng/mL	154.9 (69.5–377.2)	168
Hemoglobin, g/dL	11.8±2.3	14
Echocardiographic findings		
Left ventricular ejection fraction, %	59.4±10.4	9
Left ventricular end-diastolic dimension, mm	42.8±6.5	1
Left ventricular end-systolic dimension, mm	28.2±7.3	1
Left ventricular end-diastolic volume, mL	64.8±28.3	16
Left ventricular end-systolic volume, mL	27.8±22.0	16
Tricuspid regurgitation pressure gradient, mm Hg	38.6±16.2	22
Tricuspid regurgitation vena contracta width, mm	9.2 (7.9–11.3)	102
E/e′ (average)	11.7±6.1	114
Maximum diameter of inferior vena cava, mm	18 (14–22)	31
Left atrial diameter, mm	40.5±10.7	0
Left atrial volume index, mL/m^2	53.3 (35.4–75.3)	0

Results are expressed as mean±SD, median (interquartile range), or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD/IP, chronic obstructive pulmonary disease/interstitial pneumonia; E/e', E velocity divided by mitral annular e' velocity; and MRA, mineralocorticoid receptor antagonist.

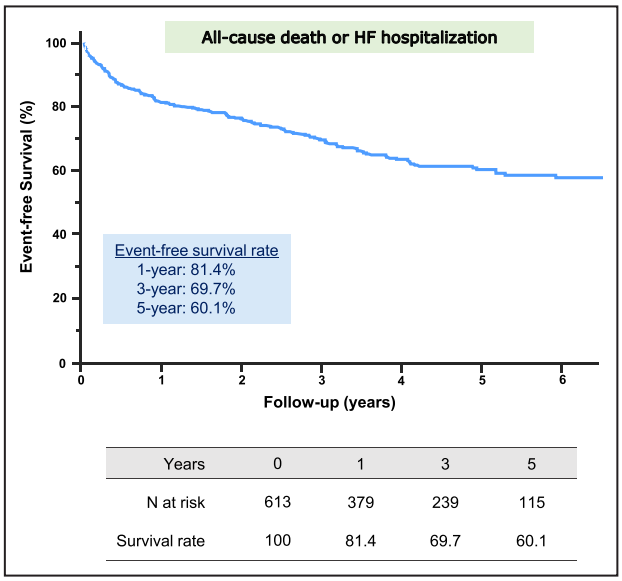


Figure 1. Kaplan-Meier survival curves for a composite of all-cause death and hospitalization for heart failure (HF).

Scores for the Risk Assessment of Patients With Isolated TR

The patients were further subdivided into groups according to 4 prognostically relevant factors, including (1) TRPG >40 mm Hg, (2) BUN >25 mg/dL, (3) albumin <3.7 g/dL, and (4) LAVi <34 mL/m^2. The baseline characteristics of patients stratified by the scores are shown in Table S1. Patients with higher scores tended to exhibit worse symptoms, higher B-type natriuretic peptide levels, and worse renal function. During the follow-up, patients with all 4 risk factors showed the highest event rate among the groups (Figure 2A). The adverse event rate also increased with the number of risk factors present (score 4 versus score 0 [reference]: adjusted HR, 8.39 [95% CI, 3.21–21.9]; P<0.001; score 3: adjusted HR, 4.88 [95% CI, 2.05–11.6]; P<0.001; score 2: adjusted HR, 2.74 [95% CI, 1.17–6.41]; P=0.02; score 1: adjusted HR, 1.29 [95% CI, 0.54–3.06];

Table 2. Univariate and Multivariable Analyses for Predicting Adverse Events in Patients With Isolated Severe TR

Variable	Univariate analyses		Multivariable analyses	
	Hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Age	1.04 (1.03–1.06)	<0.001	1.04 (1.02–1.07)	0.001
Male sex	1.64 (1.22–2.19)	0.001	2.16 (1.26–3.70)	0.005
Body mass index (>median)	0.81 (0.60–1.09)	0.156	…	…
Symptomatic	1.86 (1.36–2.54)	<0.001	1.52 (0.74–3.11)	0.256
Atrial fibrillation or flutter	0.95 (0.71–1.28)	0.738	0.84 (0.49–1.45)	0.541
ACEI/ARB	0.95 (0.67–1.35)	0.770	…	…
β-Blocker	1.04 (0.75–1.44)	0.828	…	…
MRA	1.42 (1.02–1.96)	0.037	1.37 (0.74–2.53)	0.310
Diuretics	1.43 (1.06–1.94)	0.019	0.69 (0.33–1.42)	0.311
Examination during hospitalization	3.07 (2.27–4.14)	<0.001	1.42 (0.82–2.47)	0.210
Albumin	0.46 (0.37–0.56)	<0.001	0.56 (0.36–0.95)	0.030
Acetylcholinesterase	0.992 (0.990–0.994)	<0.001	1.002 (0.998–1.01)	0.274
BUN	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.04)	0.009
Creatinine	1.14 (1.06–1.22)	<0.001	0.90 (0.76–1.07)	0.241
Sodium	0.93 (0.89–0.97)	0.001	0.95 (0.88–1.02)	0.173
Hemoglobin	0.80 (0.75–0.86)	<0.001	0.96 (0.83–1.10)	0.513
BNP	2.09 (1.51–2.88)	<0.001	1.25 (0.71–2.18)	0.444
LVEF	0.98 (0.97–0.99)	0.001	0.996 (0.97–1.02)	0.756
Left ventricular end-diastolic volume	1.01 (1.001–1.01)	0.017	0.995 (0.98–1.01)	0.451
E/e′	1.03 (1.002–1.05)	0.032	0.995 (0.96–1.04)	0.828
LAVi	1.001 (0.999–1.004)	0.380	1.01 (1.002–1.02)	0.017
TRPG	1.03 (1.02–1.03)	<0.001	1.03 (1.01–1.04)	<0.001
Maximum diameter of IVC	1.001 (0.99–1.01)	0.873	…	…

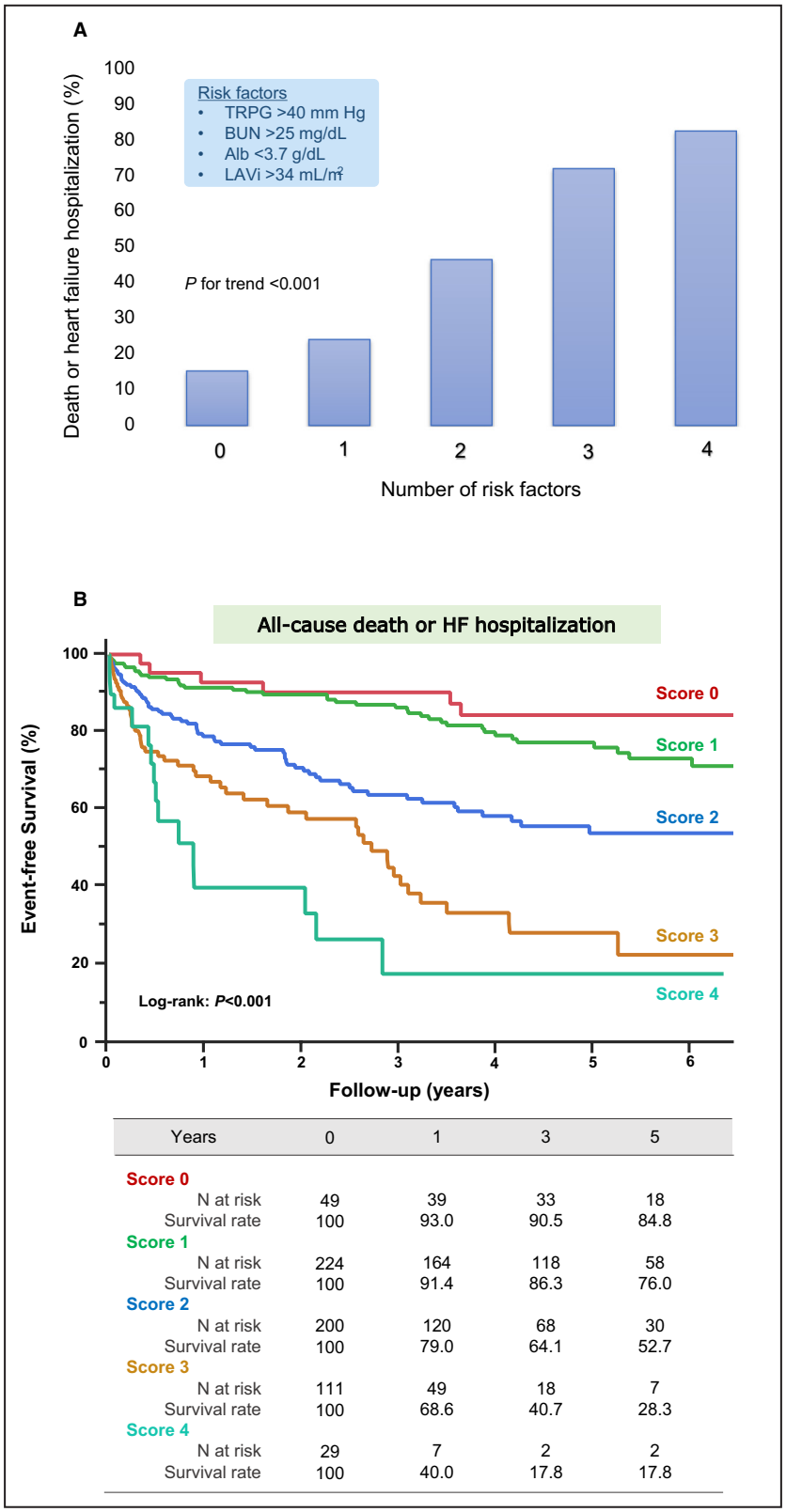
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; E/e', E velocity divided by mitral annular e' velocity; IVC, inferior vena cava; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; TR, tricuspid regurgitation; and TRPG, TR pressure gradient.

P=0.56). The Kaplan-Meier survival curve shows the graded increase of event rates according to the number of risk factors (Figure 2B).

Overall survival rate among all study patients was 86.3% at 1 year, 76.5% at 3 years, and 70.6% at 5 years (Figure 3A). The number of risk factors also shows the graded increase of risks of all-cause mortality (Figure 3B). In the multivariate analyses, older age (adjusted HR, 1.07 [95% CI, 1.04–1.11]; *P*<0.001); male sex (adjusted HR, 3.08 [95% CI, 1.68–5.67]; *P*<0.001); mineralocorticoid receptor blocker use (adjusted HR, 2.46 [95% CI, 1.21–5.01]; *P*=0.013); diuretic use (adjusted HR, 0.41 [95% CI, 0.18–0.93]; *P*=0.033); serum albumin level (adjusted HR, 0.48 [95% CI, 0.28–0.82]; *P*=0.007); BUN level (adjusted HR, 1.02 [95% CI, 1.01–1.04]; *P*=0.006); serum levels of sodium (adjusted HR, 0.92 [95% CI, 0.84–0.99]; *P*=0.031); and TRPG (adjusted HR, 1.028 [95% CI, 1.01–1.04]; *P*<0.001) remain significant factors.

Sensitivity Analyses

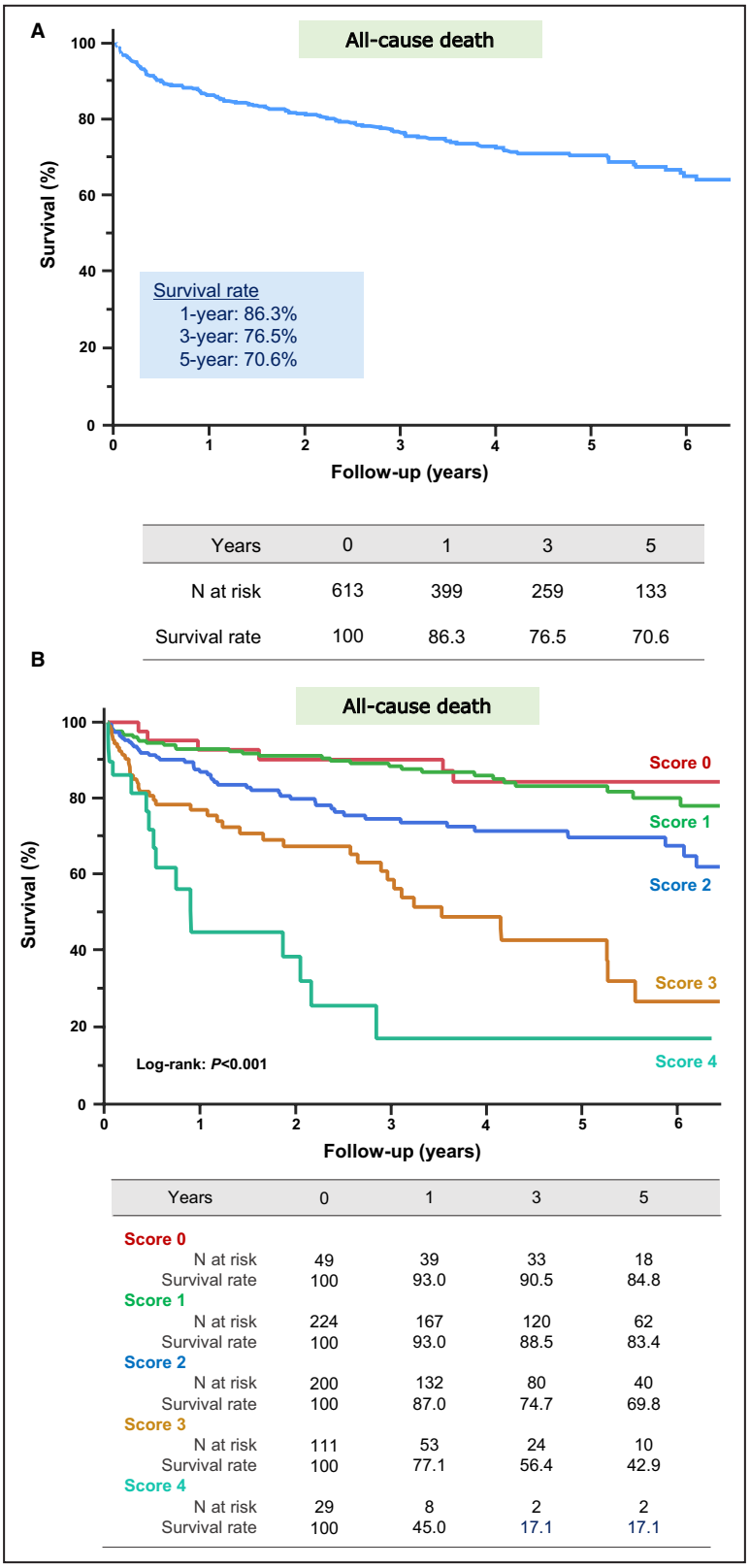
We performed sensitivity analyses to examine the generalizability of the current results. First, we excluded 55 patients with active cancer. The 5-year adverse event–free rate was 62.2%. The Kaplan-Meier curve showed a similar trend to that generated during the original analysis (Figure S2). In addition, the Kaplan-Meier curves illustrate 449 patients for whom quantitative TR data were available (Figure S3) and 277 patients without primary TR, left ventricular dysfunction, pulmonary hypertension, and history of left-sided valve disease (Figure S4). The trend was similar to that of the original analysis in both analyses. Finally, we analyzed multivariable analysis excluding B-type natriuretic peptide, which had a relatively high number of missing values. Older age (adjusted HR, 1.04 [95% CI, 1.02–1.06]; *P*<0.001); male sex (adjusted HR, 2.12 [95% CI, 1.33–3.38]; *P*=0.001); mineralocorticoid receptor blocker use (adjusted HR, 2.46 [95% CI, 1.21–5.01]; *P*=0.013); serum albumin (adjusted HR, 0.49 [95% CI, 0.33–0.73]; *P*<0.001); BUN (adjusted HR, 1.02 [95% CI, 1.01–1.04]; *P*=0.003); and TRPG (adjusted HR, 1.03 [95% CI, 1.01–1.04]; *P*<0.001) remained statistically significant and generally consistent with the original analysis.



Years	0	1	3	5
Score 0				
N at risk	49	39	33	18
Survival rate	100	93.0	90.5	84.8
Score 1				
N at risk	224	164	118	58
Survival rate	100	91.4	86.3	76.0
Score 2				
N at risk	200	120	68	30
Survival rate	100	79.0	64.1	52.7
Score 3				
N at risk	111	49	18	7
Survival rate	100	68.6	40.7	28.3
Score 4				
N at risk	29	7	2	2
Survival rate	100	40.0	17.8	17.8

Figure 2. Incidence of adverse events (A) and Kaplan-Meier survival curves for all-cause death and hospitalization for HF (B), stratified by the number of risk factors.

Alb indicates albumin; BUN, blood urea nitrogen; HF, heart failure; LAVi, left atrial volume index; and TRPG, tricuspid regurgitation pressure gradient.



Years	0	1	3	5
N at risk	613	399	259	133
Survival rate	100	86.3	76.5	70.6

Years	0	1	3	5
Score 0				
N at risk	49	39	33	18
Survival rate	100	93.0	90.5	84.8
Score 1				
N at risk	224	167	120	62
Survival rate	100	93.0	88.5	83.4
Score 2				
N at risk	200	132	80	40
Survival rate	100	87.0	74.7	69.8
Score 3				
N at risk	111	53	24	10
Survival rate	100	77.1	56.4	42.9
Score 4				
N at risk	29	8	2	2
Survival rate	100	45.0	17.1	17.1

Figure 3. Kaplan-Meier survival curves for all-cause death among all study patients (A) and those stratified by the number of risk factors (B).

DISCUSSION

In the current study, we examined the natural history and risk factors for adverse events in patients with isolated severe TR. The main findings are as follows: (1) During the median follow-up of 26.5 (interquartile range, 6.0–57.9) months, 180 patients (29.4%) experienced adverse events, a composite of all-cause death and hospitalization for heart failure. The 5-year event-free survival rate was 60.1%. (2) Multivariable analysis identified older age, male sex, higher TRPG, higher BUN level, LAVi, and lower serum albumin level as risk factors of adverse events. (3) The risk score using TRPG, BUN, LAVi, and albumin was associated with a graded increase of the adverse event rate.

Significant TR can lead to right-sided heart failure and subsequent organ damage, including liver and renal dysfunction[13] (Figure 4). Increased right atrial pressure attributable to right-sided heart failure is associated with impaired renal function,[14] which is also an independent factor in the prognosis of TR.[15–17] A congested liver causes decreased albumin levels, impaired coagulability, and poor nutritional status with reduced protein synthesis, thus putting the patients at risk of a poor systemic condition in the perioperative and postoperative periods.[18] In addition, the

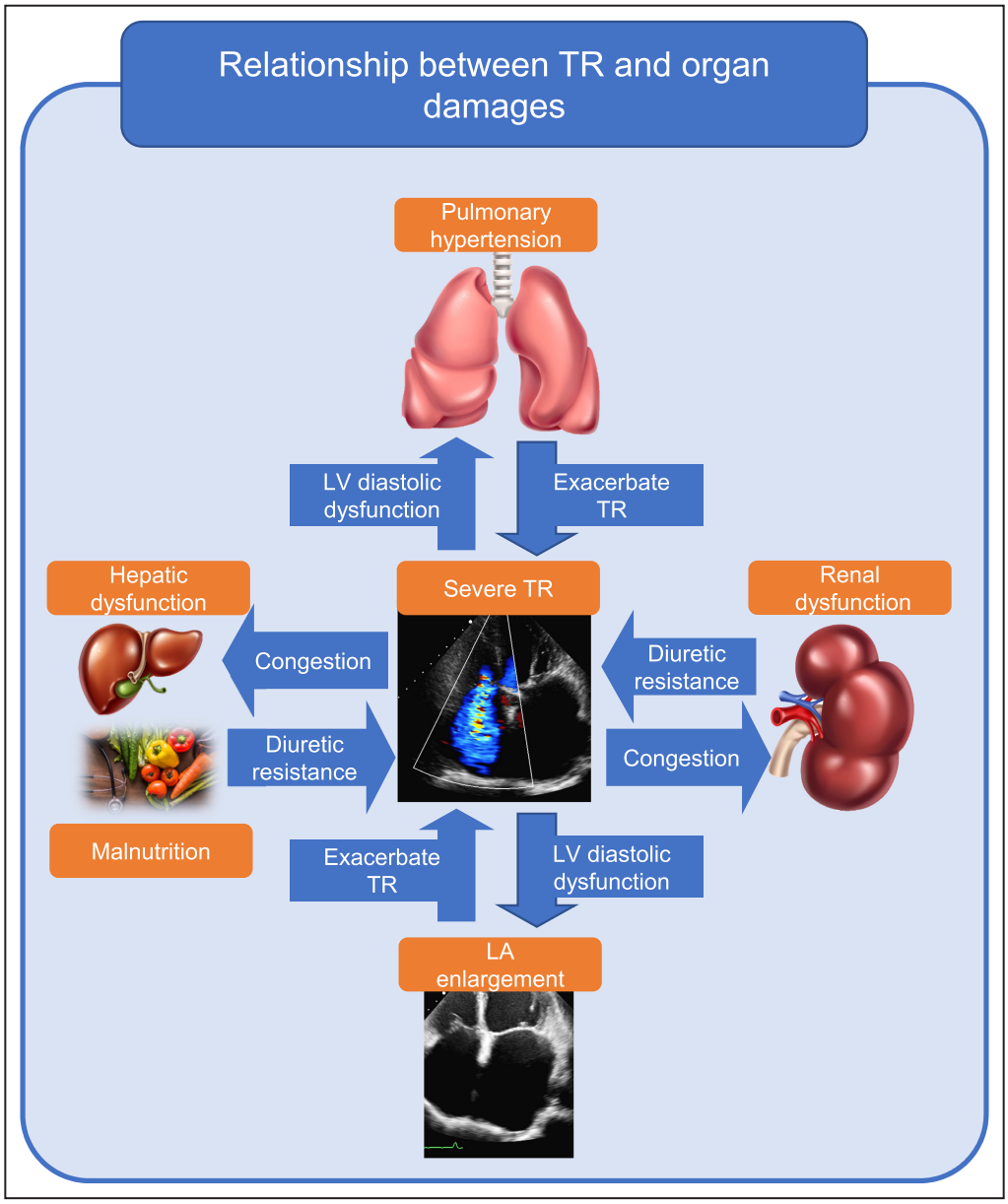


Figure 4. Diagram of association between advanced TR and multiorgan damages.
LA indicates left atrial; LV, left ventricular; and TR, tricuspid regurgitation.

importance of nutritional status has been suggested as a prognostic indicator after transcatheter tricuspid valve repair.[19] Furthermore, albumin is affected by liver function and nutritional status, as well as a wide variety of pathological conditions, including chronic inflammation and nephrosis.[20] Similarly, BUN is affected by fluid balance, gastrointestinal bleeding, metabolic abnormalities, and renal function.[21] Therefore, because they reflect on systemic conditions, we believe that BUN and albumin, not creatinine or cholinesterase, were significant predictors for worse outcomes.

Pulmonary hypertension causes right ventricular pressure overload, leading to progression of TR.[22] Conversely, TR may be a cause of pulmonary hypertension. With increasing TR, the right ventricle dilates and causes increased right ventricular diastolic pressure and, in an advanced situation, a shift of the interventricular septum toward the left ventricle. Such ventricular interdependence might cause restricted left ventricular filling and elevated left ventricular end-diastolic pressure and pulmonary artery pressure.[23] Butcher et al reported that TR reduces cardiac output and adversely affects renal function via a reduced left ventricular end-diastolic volume attributable to right ventricular enlargement.[24] However, it is difficult to determine whether pulmonary hypertension was a cause or a consequence of the TR. Left atrial enlargement is caused by volume and pressure loading of the left atrium. LAVi has been used not only to assess left atrial enlargement but also as a measure of left ventricular diastolic capacity.[25] Although TR is not directly related to LA dilation, atrial fibrillation or left ventricular diastolic dysfunction may be related to ventricular septal exhaustion, similar to the mechanism of pulmonary hypertension. The combined use of Tricuspid Annular Plane Systolic Excursion and estimated pulmonary artery systolic pressure, which reflect right ventricle–pulmonary artery coupling, is also reportedly a poor prognostic factor in patients with TR.[26]

Currently, there are no clear recommendations other than echocardiographic findings for the timing of surgical intervention for isolated severe TR. In a recent study examining all-cause mortality in patients with isolated secondary TR, the authors reported a 5-year survival rate of 47.2%,[27] which was worse than our study's rate. These differences may be explained by left ventricular ejection fraction (50%±15% versus 59%±10%), the prevalence of lung disease, and other organ involvement. Another study reported that rapid progression to severe TR was associated with higher mortality rates.[28] Fortuni et al proposed a new algorithm for grading TR, suggesting that a combined assessment of vena contracta width and effective regurgitant orifice area has prognostic value.[29]

On the basis of our results, the nutritional status, the presence of liver and renal dysfunction, and left atrial enlargement should be given more attention when considering the timing of intervention in patients with isolated severe TR. However, whether interventions based on these indicators will improve outcomes is unknown. Future studies are warranted to determine whether early intervention before the emergence of poor prognostic factors can improve outcomes in patients with severe TR.

Study Limitations

This study has several limitations. First, this is a single-center, observational, retrospective study, which is prone to inherent bias. Our study showed associations between risk factors and prognosis in patients with TR; however, the causal relationship is unclear. Despite the covariable adjustment and sensitivity analyses we performed, we could not exclude the influence of other measured and unmeasured confounders. Second, echocardiographic indexes for right ventricular function could not be investigated because of missing records. Third, we could not examine the time course of TR before the initial examination. Speed of progression is a critical perspective and a limitation that was not addressed in this study. Finally, because some clinical follow-up data were obtained from personal or telephone interviews, the data might be subject to recall bias. However, the outcomes used in this study were death or rehospitalization, hard end points deemed relatively hard to forget.

CONCLUSIONS

The prognosis of isolated severe TR is not always favorable. Careful attention should be paid to patients with isolated severe TR and concomitant risk factors, such as pulmonary hypertension, renal and/or liver dysfunction, and left atrial enlargement.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics, comorbidities, medication, and laboratory and echocardiography findings at the time of diagnosis among patient groups stratified by the number of risk factors

Number of risk factors held	0 (n=49)	1 (n=224)	2 (n=200)	3 (n=111)	4 (n=29)	p value
Characteristics/co-morbidities						
Age, years	62.5±20.3	72.0±13.5	75.4±11.5	77.3±9.9	78.9±11.6	<0.001
Male sex	14 (28.6%)	79 (35.3%)	85 (42.5%)	43 (38.7%)	10 (34.5%)	0.349
Hypertension	11 (22.4%)	62 (31%)	78 (42.2%)	42 (39.6%)	14 (48.3%)	0.056
Diabetes mellitus	2 (4.8%)	22 (11%)	37 (20%)	20 (18.9%)	12 (41.4%)	<0.001
Hyperlipidemia	0 (0.0%)	0 (0.0%)	6 (3.2%)	9 (8.5%)	4 (13.8%)	<0.001
Chronic kidney disease	0 (0.0%)	6 (3%)	17 (9.2%)	26 (24.5%)	11 (37.9%)	<0.001
Atrial fibrillation/flutter	5 (10.2%)	111 (49.6%)	98 (49%)	58 (52.3%)	10 (34.5%)	<0.001
Pacemaker/implantable cardioverter defibrillators	1 (2.4%)	17 (8.5%)	24 (13%)	16 (15.1%)	0 (0.0%)	0.027
Ischemic heart disease	4 (9.5%)	21 (10.5%)	30 (16.2%)	14 (13.2%)	3 (10.3%)	0.485
COPD/IP	3 (7.1%)	13 (6.5%)	20 (10.8%)	6 (5.7%)	2 (6.9%)	0.475
Surgery for left-side valve disease	8 (16.7%)	60 (26.9%)	47 (23.5%)	31 (27.9%)	3 (10.3%)	0.181

Active malignancy	4 (8.2%)	16 (7.1%)	16 (8.0%)	16 (14.4%)	3 (10.3%)	0.268
Symptomatic	16 (32.7%)	113 (50.4%)	122 (61%)	77 (69.4%)	19 (65.5%)	<0.001
Medication at diagnosis						
ACE-I/ARB	4 (11.1%)	40 (22%)	56 (30.1%)	24 (23.3%)	5 (17.9%)	0.067
Beta-blocker	8 (22.2%)	52 (28.6%)	57 (31.3%)	29 (28.2%)	9 (32.1%)	0.836
MRA	4 (11.1%)	41 (22.5%)	52 (28.6%)	24 (23.3%)	6 (21.4%)	0.221
Diuretics	7 (19.4%)	72 (39.6%)	95 (52.7%)	51 (49.5%)	15 (53.6%)	0.002
Laboratory findings						
Total bilirubin, mg/dL	0.6 [0.5, 0.8]	0.7 [0.5, 1.0]	0.7 [0.5, 1.0]	0.7 [0.4, 1.0]	0.7 [0.4, 0.9]	0.298
Albumin, g/dL	4.1±0.3	4.0±0.6	3.5±0.6	3.2±0.6	2.8±0.6	<0.001
AST, IU/L	22 [19, 28]	24 [21, 30]	26 [20, 35]	26 [20, 33]	28 [23, 38]	0.047
ALT, IU/L	16 [14, 25]	17 [13, 24]	19 [13, 28]	16 [12, 25]	18 [14, 31]	0.209
CHE, IU/L	264±70	255±73	218±71	179±71	142±48	<0.001
BUN, mg/dL	14.6±3.7	16.6±4.4	22.3±11.3	31.8±19.9	42.9±15.5	<0.001
Creatinine, mg/dL	0.73 [0.59, 0.86]	0.74 [0.64, 0.93]	0.90 [0.68, 1.15]	1.11 [0.74, 1.78]	1.60 [1.11, 2.19]	<0.001
Na, mEq/L	139±4	140±3	139±4	138±3	138±4	0.002
K, mEq/L	4.1±0.4	4.2±0.5	4.1±0.5	4.2±0.8	4.3±0.6	0.474
Cl, mEq/L	105±4	104±4	104±4	104±5	104±6	0.757
BNP, ng/mL	56.2	103.9	195.8	279.5	490.4	<0.001

	[37.6, 89.4]	[60.2, 207.1]	[96.9, 411.8]	[121.2, 663.8]	[118.5, 1190.0]	
Hemoglobin, g/dL	12.8±1.8	12.9±2.0	11.6±2.0	10.4±2.2	9.8±1.9	<0.001
Echocardiographic findings						
Left ventricular ejection fraction, %	61.3±10.1	59.9±9.6	58.6±11.1	59.8±10.0	56.2±13.0	0.183
Left ventricular end-diastolic dimension, mm	39.7±6.7	42.7±5.6	43.0±7.0	43.7±7.1	44.0±6.7	0.006
Left ventricular end-systolic dimension, mm	25.4±5.7	28.0±6.3	28.8±8.2	28.3±7.6	30.1±7.9	0.027
Left ventricular end-diastolic volume, mL	55.8±21.9	62.1±20.4	66.9±34.3	68.7±30.9	70.2±29.9	0.029
Left ventricular end-systolic volume, mL	22.1±14.0	25.7±14.5	30.3±29.3	28.8±20.0	33.0±25.0	0.049
Tricuspid regurgitation pressure gradient, mmHg	30.3±6.2	33.5±13.8	39.3±16.8	47.1±17.2	52.4±10.8	<0.001
Tricuspid regurgitation vena contracta width, mm	7.9 [5.9, 9.2]	8.2 [7.1, 10.0]	9.0 [7.5, 10.8]	9.3 [7.5, 11.4]	9.8 [7.6, 12.0]	0.003
E/e' (average)	8.3±3.1	10.8±5.6	12.1±6.5	13.9±6.8	13.8±3.7	<0.001
Maximum diameter of inferior vena cava, mm	14 [11, 19]	18 [14, 21]	19 [14, 23]	19 [15, 23]	19 [16, 21]	<0.001
Left atrial diameter, mm	30.0±7.9	40.8±10.5	41.1±11.1	42.8±9.3	42.8±8.9	<0.001
Left atrial volume index, mL/m^2	26.4 [13.1, 28.6]	50.9 [35.5, 76.7]	56.3 [38.4, 76.2]	62.2 [48.2, 75.6]	60.7 [52.0, 82.1]	<0.001

Data are presented as n (%), mean ±SD, or median (interquartile range).

ACEI/ARB, angiotensin-converting enzyme inhibitor /angiotensin receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; ChE,

acetylcholinesterase; CI, confidence interval; HR, hazard ratio; IVC, inferior vena cava; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, sodium; TRPG, tricuspid regurgitation pressure gradient.

SUPPLEMENTAL FIGURE LEGEND

Figure S1. Flow chart showing study design and patient selection.

AR, aortic regurgitation; AS, aortic stenosis; Echo, echocardiography; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation.

Figure S2. Kaplan-Meier curves for a composite of all-cause death and hospitalization for heart failure among patients without active cancer (A) and those stratified by number of risk factors (B).

TR, tricuspid regurgitation.

Figure S3. Kaplan-Meier curves for a composite of all-cause death and hospitalization for heart failure among patients with available quantitative TR (A) and those stratified by number of risk factors (B).

TR, tricuspid regurgitation.

Figure S4. Kaplan-Meier curves for a composite of all-cause death and hospitalization for heart failure among patients without primary TR, left ventricular dysfunction, pulmonary hypertension, and history of left-side valve disease (A) and for those stratified by number of risk factors (B).

TR, tricuspid regurgitation.

Figure S1.

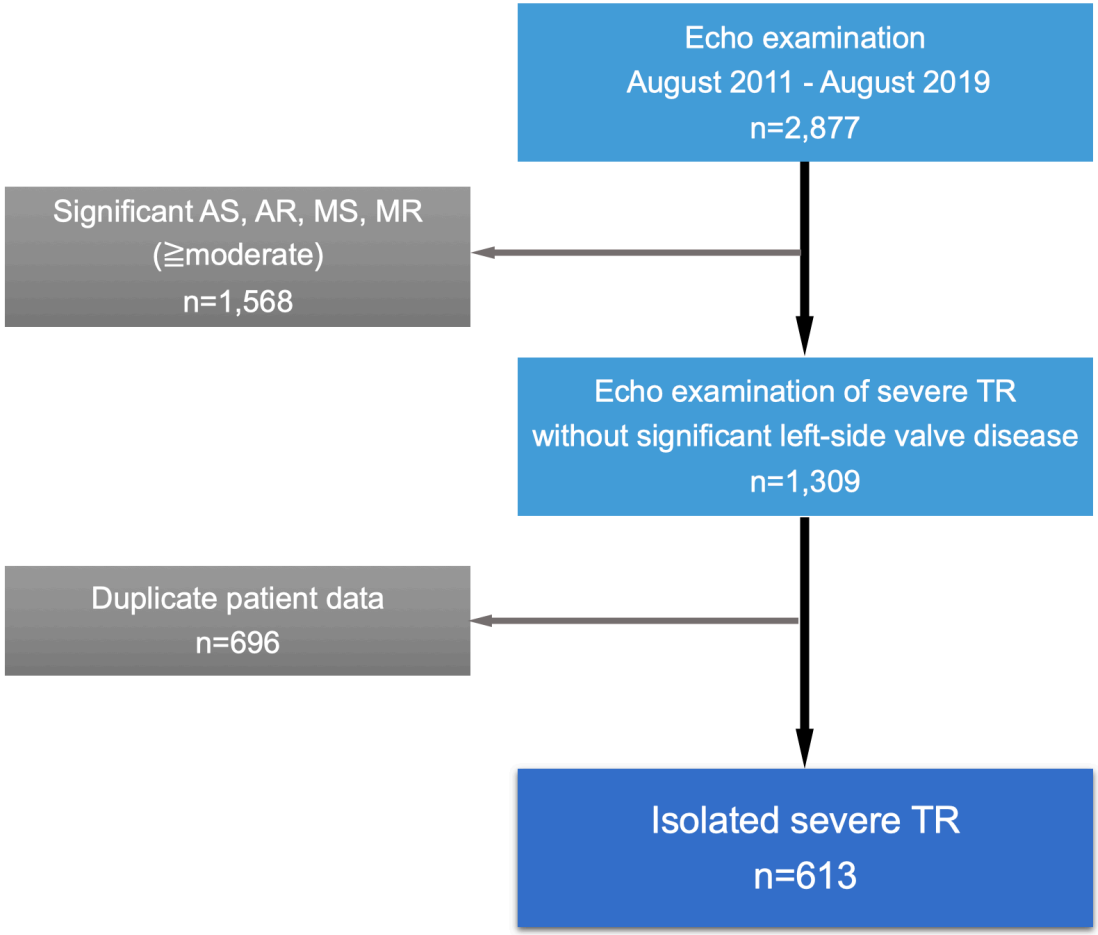
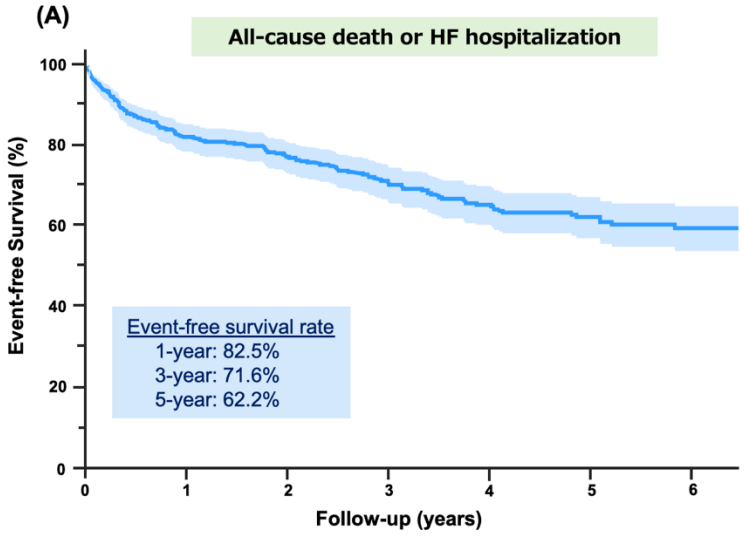
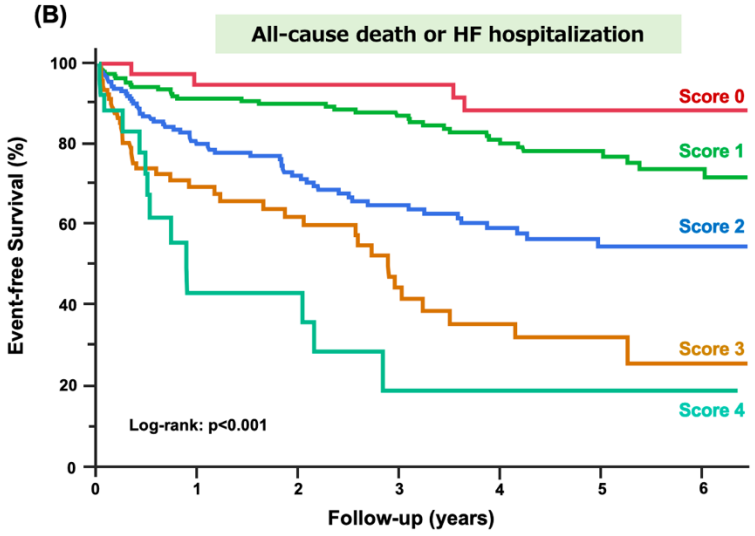

Echo examination
August 2011 - August 2019
n=2,877
Significant AS, AR, MS, MR
(≧moderate)
n=1,568
Echo examination of severe TR
without significant left-side valve disease
n=1,309
Duplicate patient data
n=696
Isolated severe TR
n=613

Figure S2.

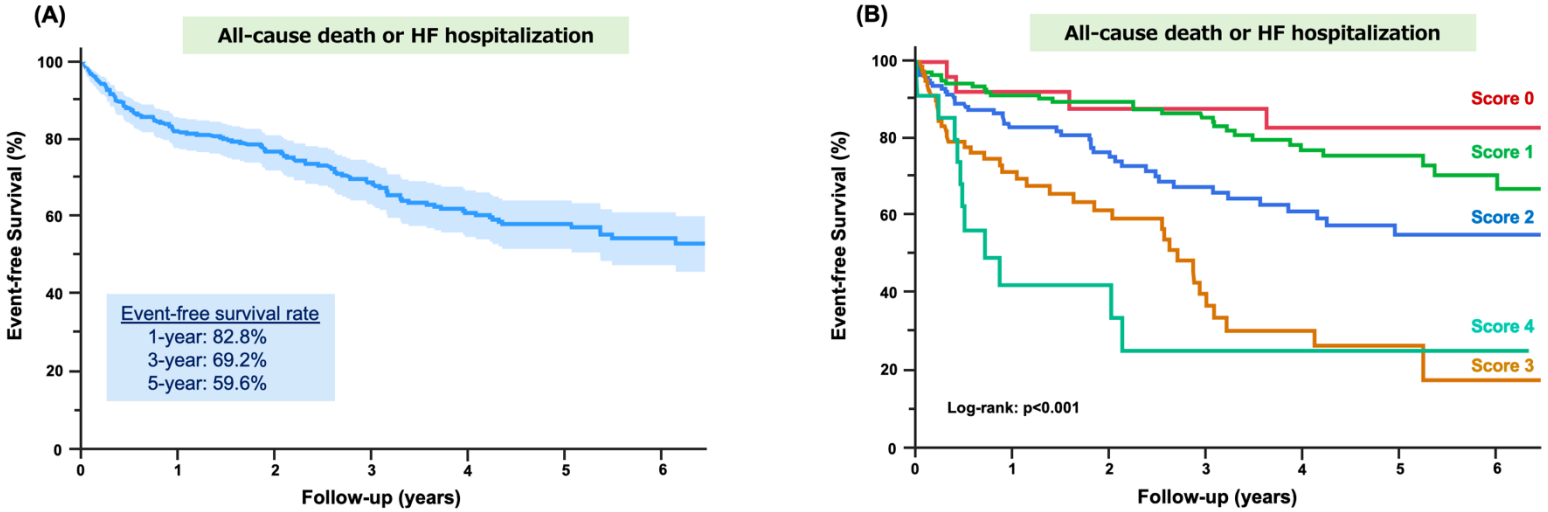


Years	0	1	3	5
N at risk	558	352	226	111
Survival rate	100	82.5	71.6	62.2



Years	0	1	3	5
Score 0				
N at risk	45	37	32	17
Survival rate	100	94.9	94.9	88.8
Score 1				
N at risk	208	153	110	55
Survival rate	100	91.4	87.2	77.0
Score 2				
N at risk	184	113	67	30
Survival rate	100	80.3	65.3	53.6
Score 3				
N at risk	95	42	15	7
Survival rate	100	69.6	42.0	32.5
Score 4				
N at risk	26	7	2	2
Survival rate	100	43.4	19.3	19.3

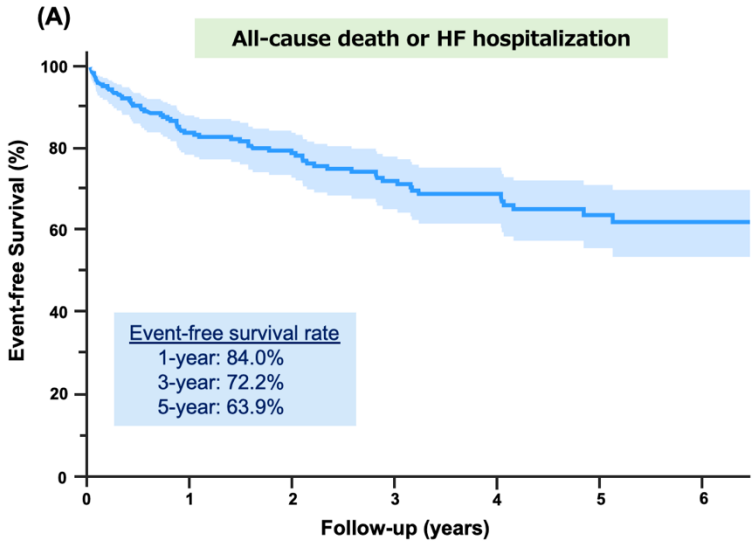
Figure S3.



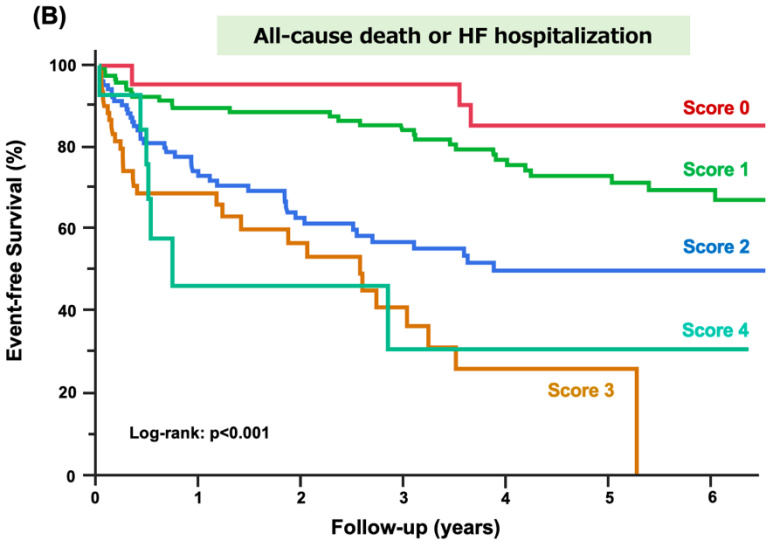
Years	0	1	3	5
N at risk	449	274	158	73
Survival rate	100	82.8	69.2	59.6

Years	0	1	3	5
Score 0				
N at risk	30	23	19	12
Survival rate	100	92.3	87.9	83.0
Score 1				
N at risk	158	113	77	32
Survival rate	100	91.4	85.6	75.8
Score 2				
N at risk	152	91	48	23
Survival rate	100	83.2	67.7	56.4
Score 3				
N at risk	86	41	12	4
Survival rate	100	71.6	37.1	26.7
Score 4				
N at risk	23	6	2	2
Survival rate	100	42.4	25.4	25.4

Figure S4.



Years	0	1	3	5
N at risk	277	168	96	40
Survival rate	100	84.0	72.2	63.9



Years	0	1	3	5
Score 0				
N at risk	23	17	12	8
Survival rate	100	89.7	83.7	83.7
Score 1				
N at risk	98	68	45	15
Survival rate	100	94.0	89.4	85.0
Score 2				
N at risk	92	57	29	13
Survival rate	100	86.1	72.8	59.4
Score 3				
N at risk	49	23	10	4
Survival rate	100	69.1	45.1	30.4
Score 4				
N at risk	15	3	0	0
Survival rate	100	34.3	-	-