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ORIGINAL ARTICLE

Tricuspid regurgitation in elderly patients with acute heart failure: insights from the KCHF registry

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Abstract

Aims Several studies demonstrated that tricuspid regurgitation (TR) is associated with poor clinical outcomes. However, data on patients with TR who experienced acute heart failure (AHF) remains scarce. The purpose of this study is to evaluate the association between TR and clinical outcomes in patients admitted with AHF, using a large-scale Japanese AHF registry.

Methods and results The current study population consisted of 3735 hospitalized patients due to AHF in the Kyoto Congestive Heart Failure (KCHF) registry. TR grades were assessed according to the routine clinical practice at each participating centre. We compared the baseline characteristics and outcomes according to the severity of TR. The primary outcome was all-cause death. The secondary outcome was hospitalization for heart failure (HF). The median age of the entire study population was 80 (interquartile range: 72–86) years. One thousand two hundred five patients (32.3%) had no TR, while mild, moderate, and severe TR was found in 1537 patients (41.2%), 776 patients (20.8%), and 217 patients (5.8%), respectively. Pulmonary hypertension, significant mitral regurgitation, and atrial fibrillation/flutter were strongly associated with the development of moderate/severe of TR, while left ventricular ejection fraction <50% was inversely associated with it. Among 993 patients with moderate/severe TR, the number of patients who underwent surgical intervention for TR within 1 year was only 13 (1.3%). The median follow-up duration was 475 (interquartile range: 365–653) days with 94.0% follow-up at 1 year. As the TR severity increased, the cumulative 1 year incidence of all-cause death and HF admission proportionally increased ([14.8%, 20.3%, 23.4%, 27.0%] and [18.9%, 23.0%, 28.5%, 28.4%] in no, mild, moderate, and severe TR, respectively). Compared with no TR, the adjusted risks of patients with mild, moderate, and severe TR were significant for all-cause death (hazard ratio [95% confidence interval]: 1.20 [1.00–1.43], $P = 0.0498$, 1.32 [1.07–1.62], $P = 0.009$, and 1.35 [1.00–1.83], $P = 0.049$, respectively), while those were not significant for hospitalization for HF (hazard ratio [95% confidence interval]: 1.16 [0.97–1.38], $P = 0.10$, 1.19 [0.96–1.46], $P = 0.11$, and 1.20 [0.87–1.65], $P = 0.27$, respectively). The higher adjusted HRs of all the TR grades relative to no TR were significant for all-cause death in patients aged <80 years, but not in patients aged ≥80 years with significant interaction.

Conclusions In a large Japanese AHF population, the grades of TR could successfully stratify the risk of all-cause death. However, the association of TR with mortality was only modest and attenuated in patients aged 80 or more. Further research is warranted to evaluate how to follow up and manage TR in this elderly population.

Keywords Acute heart failure; Tricuspid regurgitation; Tricuspid valve surgery; Elderly

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Introduction

Traditionally, the tricuspid valve has been referred to as 'the forgotten valve', because most tricuspid regurgitation (TR) is secondary to other cardiac diseases such as left-sided valvular heart disease or pulmonary hypertension and the impact of TR was not acknowledged by the field as an independent predictor of mortality. However, more light has been recently shed on TR, because isolated TR in elderly patients with atrial fibrillation has been increasing,[1] especially in Japan, where the society has been rapidly aging. Moreover, transcatheter interventions for TR is gradually being used in the US and European countries and suggested improving clinical outcomes of TR patients.[2] However, considering that right heart diseases including TR progress slowly, and are generally less likely to present sudden severe symptoms, it is difficult to determine what patients are appropriate candidate and when is the best timing for tricuspid valve interventions. Therefore, no clear recommendations have been established in the current guidelines.[3,4]

Several studies demonstrated that TR is associated with poor prognosis. However, the prevalence, aetiology, and impact of TR considerably vary across studies due to the differences in the study designs and inclusion criteria.[5–12] Previous large studies evaluating the association between TR and mortality were mainly based on echocardiographic databases or national medical databases with minimal exclusion criteria[5–8]; however, detailed clinically meaningful information was limited in such large databases. On the other hand, few studies focused on patients with TR who were hospitalized due to acute heart failure (AHF), even though these patients are at high risk of developing recurrent heart failure (HF) and should be considered for intensive treatments. Therefore, the purpose of this study is to evaluate the association between TR and clinical outcomes in patients admitted with AHF, using the detailed clinical data from a large-scale Japanese registry.

Methods

Study design and population

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicentre cohort study enrolling consecutive patients hospitalized for AHF between October 2014 and March 2016 at 19 secondary and tertiary hospitals in Japan. In brief, we enrolled patients who presented with AHF as defined by the modified Framingham criteria and received treatment for HF involving intravenous drugs within 24 h after hospital presentation.[13–15]

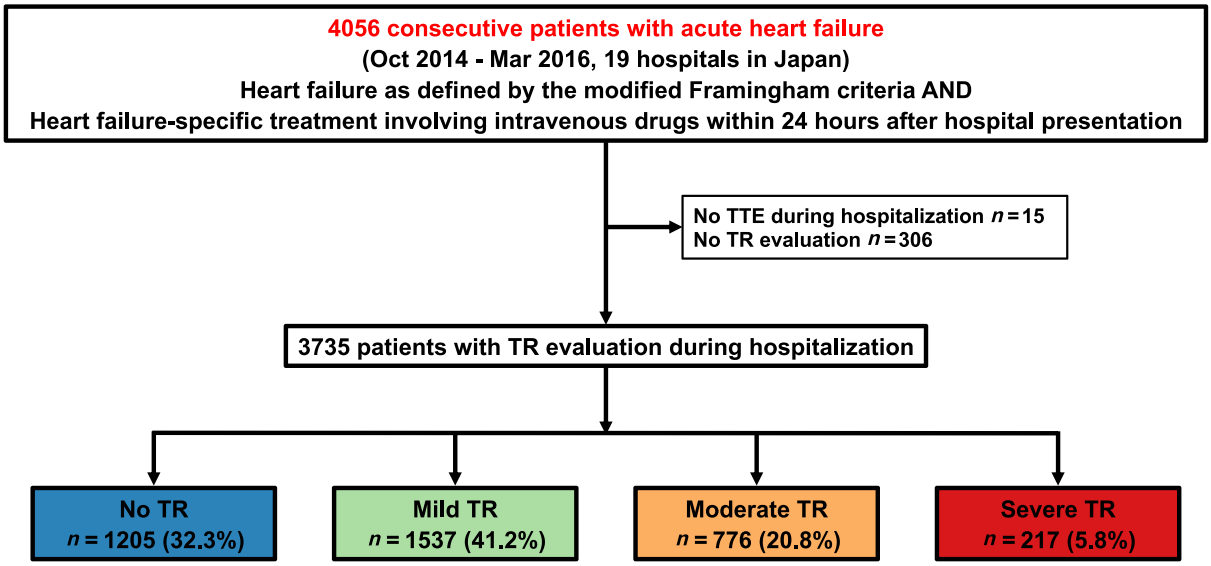
The present investigation conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethical committee at Kyoto University Hospital (local identifier: E2311) and at each participating hospital. A waiver of written informed consent from each patient was granted by the institutional review boards of Kyoto University and each participating centre based on the Japanese guidelines for epidemiological study.[16]

Among 4056 patients registered in the KCHF registry, the current study population consisted of 3735 patients whose TR severity was available during hospitalization after excluding 15 patients who did not undergo transthoracic echocardiography (TTE) evaluation and 306 patients whose TR severity was unknown (*Figure 1*). Among 872 patients with TR severity available at the 6 month (± 1 month) visit after the initial admission, the transition of TR severity was also documented.

Echocardiography and tricuspid regurgitation aetiology

According to the present guidelines, all patients underwent comprehensive two-dimensional and Doppler echocardiographic evaluation in each participating centre.[17,18] We collected the TTE data at the earliest date after admission. TR was evaluated in the apical four-chamber view, the parasternal short-axis view at the level of the aortic valve, and the right ventricular inflow view. TR grades were comprehensively assessed according to the current guideline at each participating centre and were divided into four grades: none, mild, moderate, and severe.[18] Other valvular heart diseases such as mitral regurgitation (MR) and aortic stenosis were also graded based on the current guidelines.[18,19] TR pressure gradient was estimated by TR signal using continuous-wave Doppler. Right atrial pressure was estimated by the diameter and respiratory change in diameter of the inferior vena cava. Pulmonary artery systolic pressure (PASP) was calculated from the sum of TR pressure gradient and right atrial pressure.[20]

Figure 1 Study flow chart. TR, tricuspid regurgitation; TTE, transthoracic echocardiography.



Among patients whose TR severity was mild or greater, the aetiologies of TR were hierarchically classified according to the following order based on the previous report[8]: congenital heart disease (patients with congenital origin TR such as atrial septal defect, atrioventricular septal defect, and tetralogy of Fallot, irrespective of the operative status); presence of intracardiac device (patients with any right-heart devices crossing tricuspid valve including pacemaker, implantable cardioverter defibrillator, cardiac resynchronization therapy pacemaker, and cardiac resynchronization therapy defibrillator); left-sided valvular heart disease (patients with significant [moderate/severe] left-sided valvular heart disease or those who underwent prosthetic valve implantation); left ventricular ejection fraction (LVEF) $<$ 50%; pulmonary hypertension (defined as PASP $\geq$50mmHg[6,10]); isolated TR (the remaining patients without any significant TR origin).

Data collection, definitions, and outcomes

Data on clinical characteristics and TTE were collected from hospital medical records. Clinical follow-up information was obtained from hospital medical records and/or from letters or telephone calls to patients, their relatives or their referring physicians by the site investigators or research assistants at each participating institution. Identifiable patients' data were anonymized before analysis.

The detailed definitions of baseline characteristics were previously described.[13–15] The primary outcome of the present study was all-cause death. The secondary outcome was hospitalization for HF, which was defined as hospitalization due to worsening of HF requiring intravenous drug therapy.[13] Surgical interventions for moderate or severe TR within 1 year after the index HF admission were also documented.

Statistical analysis

Categorical variables were presented as numbers and percentages, and were compared using the chi-square test. Continuous variables were presented as mean ± standard deviation or median and interquartile range (IQR) and were compared using the analysis of variance or Kruskal–Wallis test according to their distributions.

The independent correlates of moderate/severe TR were explored by the logistic regression models incorporating 10 variables which were clinically relevant or related with major TR etiologies based on the previous reports[1,10]: age $\geq$80 years, women, prior hospitalization for HF, prior myocardial infarction, atrial fibrillation or flutter, LVEF $<$50%, presence of intracardiac device, PASP $\geq$50 mmHg, moderate/severe MR, and moderate/severe aortic stenosis. The magnitude of correlation was expressed as odds ratio (OR) and their 95% confidence interval (CI).

The cumulative incidences of the outcomes were estimated with the Kaplan–Meier method according to the severity and aetiologies of TR, and the differences were assessed with the log-rank test. The date of the index AHF admission was regarded as time zero for clinical follow-up. The effects of the mild, moderate, and severe TR groups, respectively, relative to no TR group for the outcomes were estimated by the Cox proportional hazard models and were expressed as hazard ratios (HRs) and their 95% CIs. In the multivariable Cox proportional hazard models, we incorporated dummy-coded

TR status together with the 21 post-hoc clinically relevant risk-adjusting variables consistent with our previous report[15] (*Table 1*). Continuous risk-adjusting variables were dichotomized by the clinically meaningful reference values to make proportional hazard assumptions robust. Missing data were excluded when constructing multivariable models. Sensitivity analyses for the primary and secondary outcomes were performed in patients who underwent TTE within 7 days after admission. To investigate coherency of the multivariable Cox models, subgroup analyses for the primary outcome were performed in the subgroups stratified by the same 10 post-hoc variables as used in the logistic regression models. We estimated the interactions between the subgroup factors and the effects of TR on clinical outcomes.

Statistical analyses were conducted with R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). All *P* values were two-tailed, and the threshold of P values for significance was $P < 0.05$.

Results

Baseline characteristics

TTE was performed at the median of 2 days after AHF admission (interquartile range: 1–7 days). Among 3735 analysed patients, 1205 patients (32.3%) had no TR. Mild, moderate, and severe TR was found in 1537 patients (41.2%), 776 patients (20.8%), and 217 patients (5.8%), respectively (*Figure 1*). Among 872 patients whose transition of TR severity was available, the number of patients in each severity of TR was similar between the initial hospitalization and the 6 month visit (*Figure S1*). The most prevalent aetiology of TR was left-sided valvular heart disease (44.1%), followed by LVEF <50% (21.5%), and isolated TR (18.1%) (*Table S1*).

The median age of the entire study population was 80 (IQR: 72–86) years. Regarding baseline characteristics, patients with higher grades of TR were older, more often women, had lower body mass index, and less often presented with acute coronary syndrome than those without TR. They had higher prevalence of prior medical history, including hospitalization for HF, atrial fibrillation or flutter, dementia, and presence of intracardiac device. Meanwhile, they had less typical risk factors associated with atherosclerotic cardiovascular disease such as hypertension, dyslipidaemia, diabetes mellitus, and current smoking. Patients with greater severity of TR were more likely to present peripheral oedema and jugular venous distention, while less likely to present orthopnoea. In terms of laboratory data, patients with higher grades of TR had lower levels of haemoglobin, albumin, and estimated glomerular filtration rate, and had higher levels of liver enzymes, while brain natriuretic peptide and N-terminal pro-brain natriuretic peptide levels were not significantly different across the groups. As the severity of TR increased, PASP and the prevalence of concomitant moderate/severe MR became prominently higher, although left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and the prevalence of reduced LVEF became lower. Patients with more severe TR were more often prescribed loop diuretics, tolvaptan, and anticoagulants, whereas they were less often treated with angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, and beta-blocker (*Table 1*).

Predictors and surgical intervention for moderate/severe tricuspid regurgitation

Univariate logistic regression analysis showed the strongest association between the development of moderate/severe TR and PASP ≥50 mmHg (OR [95% CI]: 5.86 [4.83–7.12]), followed by moderate/severe MR (4.15 [3.56–4.84]), atrial fibrillation or flutter (2.69 [2.32–3.13]), and presence of intracardiac device (1.95 [1.55–2.44]) ($P < 0.001$ for all). In the multivariable model, the ORs for these four variables remained statistically significant. LVEF <50% was negatively associated with moderate/severe TR in both univariate and multivariable logistic regression models (0.68 [0.59–0.79], $P < 0.001$ and 0.66 [0.54–0.80], $P < 0.001$, respectively) (*Table 2*). Among 993 patients with moderate/severe TR, the number of patients who underwent surgical intervention for TR within 1 year was only 13 (1.3%), all of which underwent surgical intervention for TR simultaneously with aortic or mitral valve surgery, and there was no isolated tricuspid valve surgery (*Table S2*).

Outcomes with increasing severity of tricuspid regurgitation

The median follow-up duration was 475 (IQR: 365–653) days. A complete 1 year follow-up rate was obtained at 94.0%. The cumulative 1 year incidence of all-cause death was 14.8% in no TR, 20.3% in mild TR, 23.4% in moderate TR, and 27.0% in severe TR (Log-rank $P < 0.001$) (*Figure 2A*). The higher unadjusted risk of mild, moderate, and severe TR, respectively, relative to no TR was significant for all-cause death (HR [95% CI]: 1.35 [1.15–1.58], 1.69 [1.42–2.02], and 1.93 [1.48–2.50], $P < 0.001$ for all) (*Table 3*). Even after adjusting for confounders, the higher risk of mild, moderate, and severe TR, respectively, relative to no TR remained significant (HR [95% CI]: 1.20 [1.00–1.43], $P = 0.0498$, 1.32 [1.07–1.62], $P = 0.009$, and 1.35 [1.00–1.83], $P = 0.049$) (*Table 3*).

As the severity of TR increased, the cumulative 1 year incidence of hospitalization for HF also increased (18.9% in no TR, 23.0% in mild TR, 28.5% in moderate TR, and 28.4% in severe TR) (*Table 3*). The higher unadjusted risk of mild, moder-

Table 1 Baseline characteristics

	No TR $N = 1205$	Mild TR $N = 1537$	Moderate $N = 776$	Severe TR $N = 217$	*P* value	Missing values
Clinical characteristics						
Age, years	78.0 (68.0–84.0)	81.0 (73.0–86.0)	82.0 (75.0–87.0)	83.0 (75.0–87.0)	<0.001	0
Age ≥80 years*	521 (43.2%)	841 (54.7%)	459 (59.1%)	139 (64.1%)	<0.001	0
Women*	475 (39.4%)	686 (44.6%)	398 (51.3%)	116 (53.5%)	<0.001	0
Body mass index, kg/m^2	23.6 ± 4.8	22.5 ± 4.1	22.3 ± 4.4	22.3 ± 4.5	<0.001	179
Body mass index <22 kg/m^2*	456 (39.9%)	728 (49.7%)	368 (49.5%)	108 (52.7%)	<0.001	179
Aetiology						
Acute coronary syndrome*	131 (10.9%)	60 (3.9%)	22 (2.8%)	1 (0.5%)	<0.001	0
Medical history						
Prior hospitalization for heart failure*	350 (29.5%)	543 (35.8%)	322 (42.0%)	101 (47.2%)	<0.001	54
Hypertension*	950 (78.8%)	1093 (71.1%)	533 (68.7%)	123 (56.7%)	<0.001	0
Dyslipidaemia	538 (44.6%)	564 (36.7%)	267 (34.4%)	65 (30.0%)	<0.001	0
Diabetes mellitus*	560 (46.5%)	521 (33.9%)	235 (30.3%)	64 (29.5%)	<0.001	0
Prior myocardial infarction*	318 (26.4%)	327 (21.3%)	157 (20.2%)	29 (13.4%)	<0.001	0
Prior PCI or CABG	354 (29.4%)	395 (25.7%)	163 (21.0%)	35 (16.1%)	<0.001	0
Prior stroke*	198 (16.4%)	226 (14.7%)	128 (16.5%)	46 (21.2%)	0.09	0
Atrial fibrillation or flutter*	290 (24.1%)	676 (44.0%)	438 (56.4%)	152 (70.0%)	<0.001	0
Ventricular fibrillation or tachycardia	34 (2.8%)	64 (4.2%)	31 (4.0%)	11 (5.1%)	0.19	0
Liver cirrhosis	13 (1.1%)	20 (1.3%)	11 (1.4%)	7 (3.2%)	0.10	0
Chronic lung disease*	159 (13.2%)	205 (13.3%)	96 (12.4%)	32 (14.7%)	0.81	0
Malignancy	173 (14.4%)	215 (14.0%)	125 (16.1%)	28 (12.9%)	0.49	0
Dementia	184 (15.3%)	274 (17.8%)	164 (21.1%)	54 (24.9%)	<0.001	0
Presence of intracardiac device	58 (4.8%)	160 (10.4%)	106 (13.7%)	37 (17.1%)	<0.001	0
Pacemaker	37 (3.1%)	97 (6.3%)	76 (9.8%)	26 (12.0%)	<0.001	0
ICD	12 (1.0%)	29 (1.9%)	12 (1.5%)	2 (0.9%)	0.27	0
CRTP	3 (0.2%)	7 (0.5%)	5 (0.6%)	5 (2.3%)	0.01	0
CRTD	6 (0.5%)	28 (1.8%)	15 (1.9%)	5 (2.3%)	0.009	0
Current smoking*	191 (16.3%)	194 (12.8%)	56 (7.3%)	14 (6.5%)	<0.001	69
Social backgrounds						
Poor medical adherence	229 (19.0%)	255 (16.6%)	108 (13.9%)	36 (16.6%)	0.03	0
With occupation	228 (18.9%)	171 (11.1%)	72 (9.3%)	11 (5.1%)	<0.001	0
Public assistance	64 (5.3%)	95 (6.2%)	36 (4.6%)	13 (6.0%)	0.46	0
Living alone*	255 (21.2%)	337 (21.9%)	159 (20.5%)	52 (24.0%)	0.68	0
Institution for aged or hospital	75 (6.2%)	94 (6.1%)	52 (6.7%)	13 (6.0%)	0.95	0
Daily life activities						
Ambulatory*	987 (82.7%)	1229 (80.7%)	576 (75.2%)	149 (69.6%)	<0.001	38
Use of wheelchair (outdoor only)	71 (5.9%)	116 (7.6%)	67 (8.7%)	25 (11.7%)	0.01	38
Use of wheelchair (outdoor and indoor)	103 (8.6%)	126 (8.3%)	83 (10.8%)	33 (15.4%)	0.003	38
Bedridden	33 (2.8%)	52 (3.4%)	40 (5.2%)	7 (3.3%)	0.04	38
Vital signs at presentation						
Systolic blood pressure, mmHg	157.6 ± 38.6	146.9 ± 33.1	139.6 ± 31.6	130.1 ± 24.3	<0.001	12
Systolic blood pressure <90 mmHg*	26 (2.2%)	42 (2.7%)	26 (3.4%)	11 (5.1%)	0.08	9
Heart rate, b.p.m.	99.2 ± 27.1	95.8 ± 27.6	93.3 ± 27.8	88.5 ± 25.6	<0.001	23
Heart rate <60 b.p.m.*	63 (5.3%)	103 (6.8%)	63 (8.2%)	19 (8.8%)	0.04	23
NYHA class III or IV	1061 (88.8%)	1330 (86.9%)	667 (86.1%)	194 (89.4%)	0.21	17
Heart failure symptoms at presentation						
Orthopnoea	942 (82.9%)	1222 (81.1%)	565 (75.2%)	165 (76.7%)	<0.001	135
Dyspnoea on exertion	1055 (93.9%)	1442 (96.1%)	705 (94.8%)	204 (98.1%)	0.01	176

(*Continues*)

Table 1 (continued)

	No TR $N = 1205$	Mild TR $N = 1537$	Moderate $N = 776$	Severe TR $N = 217$	*P* value	Missing values
Peripheral oedema	807 (70.4%)	1162 (77.1%)	623 (82.6%)	196 (90.7%)	<0.001	119
Jugular venous distention	836 (74.6%)	1147 (80.1%)	590 (79.7%)	186 (88.6%)	<0.001	241
Laboratory tests						
BNP, pg/mL	724 (374–1305)	728 (403–1356)	731 (427–1258)	606 (356–1079)	0.06	451
NT-proBNP, pg/mL	5736 (2671–11 764)	6581 (2945–15 468)	5220 (2554–12 484)	6603 (2206–16 202)	0.19	3066
Haemoglobin, g/dL	11.9 ± 2.5	11.6 ± 2.3	11.2 ± 2.2	10.7 ± 2.1	<0.001	5
Anaemia*†	725 (60.3%)	1026 (66.8%)	560 (72.3%)	167 (77.3%)	<0.001	5
AST, IU/L	30 (22–45)	30 (22–45)	30 (22–47)	30 (23–48)	0.50	8
ALP, IU/L	253 (22–328)	262 (25–338)	272 (210–344)	317 (240–42)	<0.001	534
γ-GTP, IU/L	33 (19–65)	38 (21–71)	42 (25–82)	52 (28–94)	<0.001	495
Albumin, g/dL	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	3.3 ± 0.5	<0.001	103
Albumin <3.0 g/dL*	152 (12.8%)	191 (12.8%)	108 (14.4%)	45 (21.6%)	0.004	103
Sodium, mEq/L	139.1 ± 4.1	139.2 ± 4.2	139.0 ± 4.7	138.7 ± 4.5	0.23	12
Sodium <135 mEq/L*	148 (12.3%)	178 (11.6%)	107 (13.9%)	32 (14.9%)	0.31	12
eGFR, mL/min/1.73 m^2	46.8 (28.8–63.1)	44.5 (29.0–60.5)	42.1 (29.7–58.2)	37.8 (25.7–57.0)	0.01	6
eGFR <30 mL/min/1.73 m^2*	319 (26.5%)	410 (26.7%)	199 (25.7%)	74 (34.3%)	0.09	6
Echocardiographic parameters						
LVEDD, mm	51.9 ± 9.0	51.6 ± 9.4	50.5 ± 9.4	50.1 ± 8.8	0.001	61
LVESD, mm	40.1 ± 11.2	39.2 ± 11.5	37.8 ± 11.6	36.4 ± 10.6	<0.001	106
LAD, mm	42.7 ± 7.9	44.9 ± 8.6	46.9 ± 9.5	49.8 ± 10.1	<0.001	178
LVEF, %	44.6 ± 15.3	46.2 ± 16.5	47.8 ± 16.7	49.9 ± 15.9	<0.001	12
LVEF <50%	754 (62.8%)	868 (56.5%)	395 (51.2%)	98 (45.4%)	<0.001	12
LVEF <40%*	501 (41.6%)	591 (38.5%)	259 (33.4%)	55 (25.3%)	<0.001	12
TRPG, mmHg	25.6 ± 9.2	31.7 ± 10.3	39.3 ± 13.0	44.0 ± 17.8	<0.001	732
PASP, mmHg	29.9 ± 9.8	37.0 ± 11.4	46.7 ± 14.3	53.1 ± 18.1	<0.001	869
Moderate/severe MR	202 (16.9%)	479 (31.4%)	445 (57.8%)	127 (59.1%)	<0.001	30
Moderate/severe AS	63 (5.3%)	109 (7.1%)	58 (7.6%)	15 (6.9%)	0.14	37
Medication at discharge						
Loop diuretics	898 (77.0%)	1201 (81.4%)	627 (86.6%)	184 (92.0%)	<0.001	169
MRA	509 (43.7%)	679 (46.0%)	334 (46.1%)	94 (47.0%)	0.57	169
Thiazide	65 (5.6%)	78 (5.3%)	46 (6.4%)	20 (10.0%)	0.06	169
Tolvaptan	94 (8.1%)	141 (9.6%)	98 (13.5%)	45 (22.5%)	<0.001	169
ACE-I	318 (27.3%)	384 (26.0%)	154 (21.3%)	32 (16.0%)	<0.001	169
ARB	440 (37.7%)	500 (33.9%)	233 (32.2%)	42 (21.0%)	<0.001	169
ACE-I or ARB	754 (64.7%)	875 (59.3%)	385 (53.2%)	74 (37.0%)	<0.001	169
Beta-blocker	819 (70.2%)	1003 (68.0%)	451 (62.3%)	111 (55.5%)	<0.001	169
Digoxin	46 (3.9%)	76 (5.1%)	51 (7.0%)	25 (12.5%)	<0.001	169
Warfarin	197 (16.9%)	369 (25.0%)	245 (33.8%)	78 (39.0%)	<0.001	169
DOAC	178 (15.3%)	345 (23.4%)	181 (25.0%)	40 (20.0%)	<0.001	169

Continuous variables were expressed as mean ± standard deviation, or median (interquartile range). Categorical variables were expressed as number (percentage).
*Risk-adjusting variables selected for the Cox proportional hazard models.
†Defined using the World Health Organization criteria (haemoglobin <12.0 g/dL in women and <13.0 g/dL in men).
Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ALP, alkaline phosphatase; ARB, angiotensin II receptor blocker; AS, aortic stenosis; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CRTD, cardiac resynchronization therapy defibrillator; CRTP, cardiac resynchronization therapy pacemaker; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation peak gradient; γ-GTP, gamma-glutamyltransferase.

Table 2 Predictors for moderate/severe TR

	Unadjusted OR	*P* value	Adjusted OR	*P* value
Age ≥80 years*	1.53 (1.32–1.78)	<0.001	1.21 (1.00–1.47)	0.053
Women*	1.46 (1.26–1.69)	<0.001	1.21 (0.99–1.46)	0.06
Prior myocardial infarction*	0.75 (0.62–0.90)	0.002	0.86 (0.67–1.09)	0.22
Prior hospitalization for heart failure*	1.54 (1.32–1.79)	<0.001	1.17 (0.96–1.42)	0.12
Atrial fibrillation or flutter*	2.69 (2.32–3.13)	<0.001	2.04 (1.69–2.47)	<0.001
LVEF <50%*	0.68 (0.59–0.79)	<0.001	0.66 (0.54–0.80)	<0.001
Presence of intracardiac device*	1.95 (1.55–2.44)	<0.001	1.48 (1.11–1.96)	0.008
PASP ≥50 mmHg*	5.86 (4.83–7.12)	<0.001	5.87 (4.73–7.30)	<0.001
Moderate/severe MR*	4.15 (3.56–4.84)	<0.001	4.11 (3.40–4.97)	<0.001
Moderate/severe AS*	1.20 (0.90–1.59)	0.21	1.16 (0.80–1.68)	0.42

*Adjusting variables selected for the logistic regression models.
Abbreviations: AS, aortic stenosis; MR, mitral regurgitation; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; OR, odds ratio; TR, tricuspid regurgitation.

ate, and severe TR, respectively, relative to no TR was significant for hospitalization for HF (HR [95% CI]: 1.27 [1.08–1.48], *P* = 0.004, 1.42 [1.18–1.71], *P* < 0.001, and 1.58 [1.19–2.09], *P* = 0.001). However, the adjusted risks of all the TR grades relative to no TR were not significant (HR [95% CI]: 1.16 [0.97–1.38], *P* = 0.10, 1.19 [0.96–1.46], *P* = 0.11, and 1.20 [0.87–1.65], *P* = 0.27, respectively) (*Table 3*).

In the sensitivity analyses among 2807 patients who underwent TTE within 7 days after admission, the consistent result with the entire population was obtained (*Table S3*).

In the subgroup analyses, significant interaction between the subgroup factors and the effect of TR for all-cause death was found only for age ≥80 years or <80 years (*Figure 3*). The higher adjusted HRs of all the TR grades relative to no TR were significant for all-cause death in patients aged <80 years, but not in patients aged ≥80 years (*Figure 3*).

The cumulative 1 year incidence of all-cause death was the highest in patients classified into pulmonary hypertension followed by presence of intracardiac device and left-sided valvular heart disease. Meanwhile, presence of intracardiac device group had the highest cumulative 1 year incidence of hospitalization for HF (*Figure S2*).

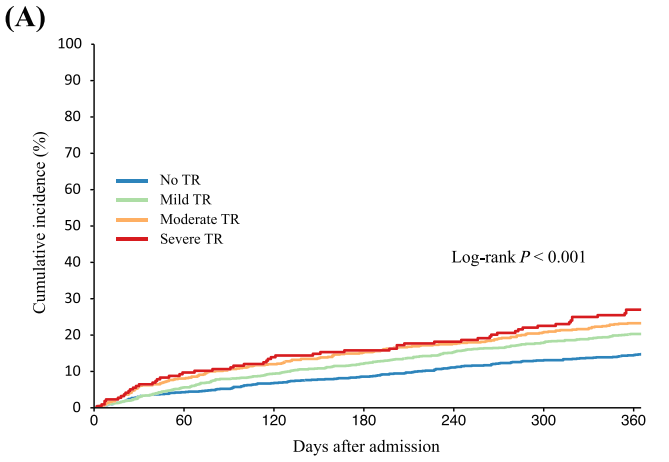
Discussion

The main findings of this study in patients with hospitalized AHF were as follows: (i) Greater severity of TR was associated with common TR aetiologies such as significant MR, pulmonary hypertension, and atrial fibrillation, while it was inversely associated with ischaemic heart disease and lower LVEF; (ii) the severity of TR successfully stratified mortality but not hospitalization for HF. Furthermore, the association between TR and mortality was attenuated in elderly patients; (iii) surgical intervention for TR was rarely performed even among patients who experienced AHF admission.

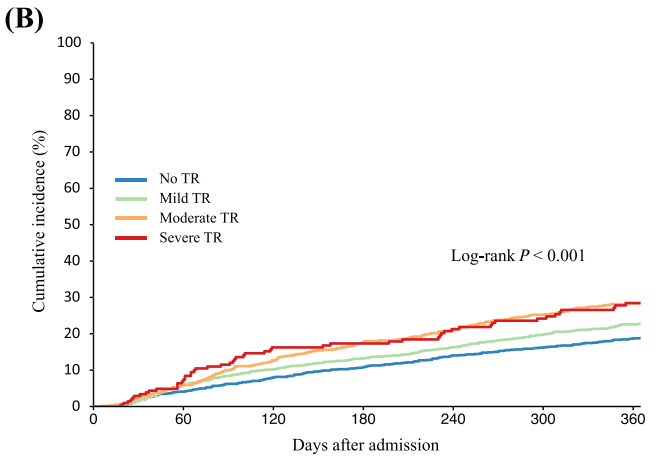
The prevalence of moderate or severe TR in this study (26.4%) is consistent with previous reports enrolling patients with HF hospitalization.[10,11] However, the major aetiologies of TR in the current study population were different from those in previous reports outside Japan. A previous study reported that left-sided valvular heart disease including MR, left ventricular dysfunction, and pulmonary hypertension were the most common causes of TR and that they were associated with increased mortality compared with other aetiologies.[6] Meanwhile, isolated TR, which is mainly derived from atrial fibrillation in elderly patients, has been of great concern in Japan secondary to the aging of the society.[21] Actually, the median age of the patients in the KCHF registry (80 years old) was remarkably higher than those in previous reports outside Japan.[14] The percentage of AHF due to ischaemic heart disease (33%) and that of patients with reduced LVEF (LVEF <40%: 38%) were much lower compared with other previous AHF registries.[14] These differences could lead to the relatively high prevalence of isolated TR (18.1%), of which LVEF was preserved. This might explain the inverse association of the severity of TR with ischaemic heart disease and lower LVEF in this study because patients with higher grades of TR were older, and often had isolated TR.

Previous studies in various settings demonstrated that the severity of TR could successfully stratify the prognosis,[5–12] and a similar result was also obtained in this study. Furthermore, the present study suggested that even mild TR as well as moderate or severe TR were independently associated with increased risk of mortality, even after intensive adjustment for clinically important variables. However, extreme caution should be paid to interpret this result considering the borderline 95% CIs, which may fluctuate depending on the selection of the risk-adjusting variables. The subgroup analysis in age showed that TR severity was independently associated with mortality only in patients less than 80 years old with significant interaction, partly because the relative impact of TR might be attenuated in elderly patients with multiple concomitant diseases and frailty. Mutlak et al. reported that significant TR was associated with greater risk for HF readmission or mortality only when it developed with concomitant pulmonary hypertension after multivariable

Figure 2 The cumulative 1 year incidence stratified with the severity of TR. *(A)* all-cause death, and *(B)* hospitalization for heart failure. TR = tricuspid regurgitation.



Interval	0 days	30 days	90 days	180 days	1 year
No TR group					
Number of patients with event		37	62	101	172
Number of patients at risk	1205	1152	1111	1057	961
Cumulative incidence		3.1%	5.2%	8.6%	14.8%
Mild TR group					
Number of patients with event		46	121	186	306
Number of patients at risk	1537	1481	1398	1321	1137
Cumulative incidence		3.0%	7.9%	12.2%	20.3%
Moderate TR group					
Number of patients with event		47	81	117	177
Number of patients at risk	776	726	677	635	560
Cumulative incidence		6.1%	10.5%	15.3%	23.4%
Severe TR group					
Number of patients with event		14	23	34	57
Number of patients at risk	217	203	191	179	144
Cumulative incidence		6.5%	10.6%	15.8%	27.0%



Interval	0 days	30 days	90 days	180 days	1 year
No TR group					
Number of patients with event		21	71	121	204
Number of patients at risk	1205	1136	1045	957	809
Cumulative incidence		1.8%	6.2%	10.8%	18.9%
Mild TR group					
Number of patients with event		24	123	189	314
Number of patients at risk	1537	1461	1293	1172	908
Cumulative incidence		1.6%	8.4%	13.2%	23.0%
Moderate TR group					
Number of patients with event		18	71	124	191
Number of patients at risk	776	712	617	539	429
Cumulative incidence		2.4%	10.0%	17.9%	28.5%
Severe TR group					
Number of patients with event		6	23	34	53
Number of patients at risk	217	199	171	151	112
Cumulative incidence		2.9%	11.5%	17.3%	28.4%

Table 3 Clinical outcomes

	TR grade	Number of events	Number of patients	Cumulative 1 year incidence	Unadjusted HR	*P* value	Adjusted HR	*P* value
All-cause death	None	246	1205	14.8%	Reference		Reference	
	Mild	393	1537	20.3%	1.35 (1.15–1.58)	<0.001	1.20 (1.00–1.43)	0.0498
	Moderate	241	776	23.4%	1.69 (1.42–2.02)	<0.001	1.32 (1.07–1.62)	0.009
	Severe	74	217	27.0%	1.93 (1.48–2.50)	<0.001	1.35 (1.00–1.83)	0.049
Hospitalization for heart failure	None	253	1205	18.9%	Reference		Reference	
	Mild	380	1537	23.0%	1.27 (1.08–1.48)	0.004	1.16 (0.97–1.38)	0.10
	Moderate	204	776	28.5%	1.42 (1.18–1.71)	<0.001	1.19 (0.96–1.46)	0.11
	Severe	61	217	28.4%	1.58 (1.19–2.09)	0.001	1.20 (0.87–1.65)	0.27

Abbreviations: HR, hazard ratio; TR, tricuspid regurgitation.

adjustment.[10] They also described that there was no significant difference between moderate/severe TR and trivial/mild TR groups for HF readmission or mortality in the propensity-matched cohort.[10] To address the precise association between TR and mortality in AHF patients, meticulous stratification for the patients' backgrounds may be the key.

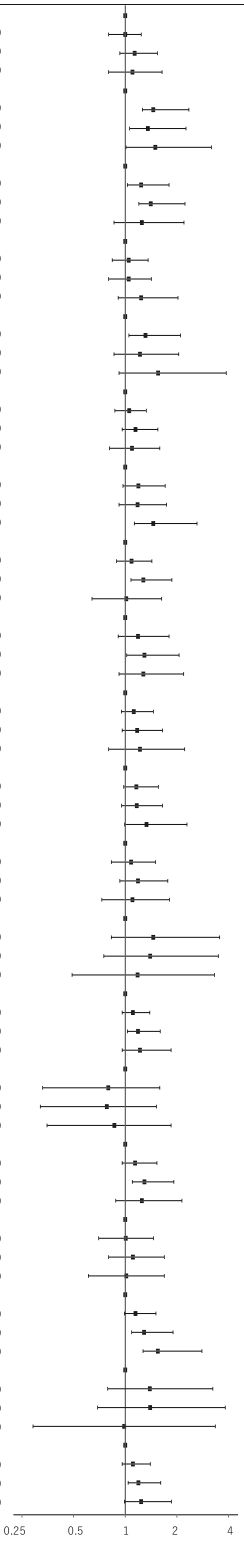
As for HF admission, the adjusted risk of each TR grade was not significant. This might be partly because the endpoint was intensively adjusted for important HF-related variables. Another possible reason was that the endpoint definition of HF admission included not only right HF but also all the HF irrespective of the underlying causes. However, this result contradicted a similar study including 2101 AHF patients by De la Espriella et al.[11] As we discussed, the main reason for this discrepancy might be the Japanese older population of AHF. TR can cause multiple organ failure such as hepatic and renal failure through venous congestion and low perfusion pressure, which is often neglected.[1] Actually, the present study demonstrated the association between greater severity of TR and impaired hepatic and renal functions. Especially, among elderly patients who are likely to have renal and hepatic impairment or to have other critical diseases like malignancy, patients with greater severity of TR might have died from other than cardiac causes before developing symptomatic HF.

In the present study, surgical intervention for TR was rare even among patients who experienced AHF admission. However, given the modest association of TR with mortality and insignificant association of TR with hospitalization for HF, conservative management for TR would not be an inappropriate strategy. In fact, tricuspid valve surgery failed to attest reduction in mortality in both a large retrospective, propensity-matched study for isolated TR and a randomized trial for patients with degenerative MR undergoing mitral valve surgery with concomitant tricuspid valve repair.[22,23] Earlier stage right HF due to TR progresses gradually and is often controllable with increased diuretics. On the other hand, a significant number of patients with moderate/severe TR experience diuretic resistance with advanced right HF, and they have already become at high risk for surgery at that time. Therefore, both attending physicians and patients might have been reluctant to choose surgery. Indeed, Vieitez et al. described that more than half of patients with severe or greater TR had at least one high surgical risk factor including PASP >50 mmHg, LVEF <35%, New York Heart Association III-IV, or older than 85 years.[24] In addition, Takahashi et al. reported that only two of 29 isolated severe TR patients with atrial fibrillation who experienced hospitalization due to right HF underwent tricuspid valve surgery in real-world clinical practice in Japan.[25] The present study also demonstrated the extremely low rate of surgery for moderate/severe TR in the broader HF population, suggesting that the presence of TR was likely to have been underestimated or even ignored. In addition, the similar prevalence of each TR severity between the initial hospitalization and the 6 month visit might be partly because of the low rate of surgical intervention for TR. A meta-analysis suggested that TR is associated with increased mortality,[12] and less invasive transcatheter intervention for TR has been reported to be a promising treatment.[26] However, given no significant adjusted excess risk of TR on mortality in elderly patients and that of HF admission in the entire study population in this study, further research is necessary in considering transcatheter intervention for TR in Japanese elderly patients.

There are several limitations in this study. First of all, due to the observational study design, there should have been residual unmeasured confounding. Although we selected the risk-adjusting variables based on the clinical relevance and consistency with our previous report,[15] their selection was post-hoc and the results might be affected depending on the selected variables. In addition, the observed event rates could be underestimated despite our maximum effort to contact the patients who lost follow-up through letters or telephone calls. Second, an echocardiographic evaluation in the core laboratory was not performed. The severity of TR was based on the assessment of each participating centre and was not validated by other observers. In addition, standardized quantitative methods for the severity of TR like vena contracta and effective regurgitant orifice area, were not performed; therefore, the recent classification for more than severe TR (massive and torrential) was not reflected.[27] Also, the aetiology of TR was not derived from direct imaging evaluation, but only from clinical information. Therefore, the novel

Figure 3 Subgroup analyses for all-cause death. HR = hazard ratio; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; MR = mitral regurgitation; AS = aortic stenosis.

Variables		TR	Number of events/patients	Adjusted HR	P for interaction
Age	≥80 years	None	172/521	Reference	0.01
		Mild	278/841	1.00 (0.80-1.24)	
		Moderate	182/459	1.20 (0.93-1.54)	
		Severe	52/139	1.15 (0.80-1.64)	
	<80 years	None	74/684	Reference	
		Mild	115/696	1.72 (1.26-2.35)	
		Moderate	59/317	1.55 (1.06-2.26)	
		Severe	22/78	1.79 (1.01-3.18)	
Gender	Women	None	96/475	Reference	0.45
		Mild	181/686	1.36 (1.03-1.80)	
		Moderate	125/398	1.64 (1.20-2.23)	
		Severe	32/116	1.38 (0.86-2.20)	
	Men	None	150/730	Reference	
		Mild	212/851	1.07 (0.84-1.36)	
		Moderate	116/378	1.07 (0.80-1.42)	
		Severe	42/101	1.36 (0.91-2.03)	
Prior myocardial infarction	Yes	None	71/318	Reference	0.51
		Mild	103/327	1.48 (1.05-2.10)	
		Moderate	53/157	1.33 (0.86-2.05)	
		Severe	12/29	1.89 (0.92-3.88)	
	No	None	175/887	Reference	
		Mild	290/1210	1.08 (0.87-1.33)	
		Moderate	188/619	1.22 (0.96-1.55)	
		Severe	62/188	1.14 (0.81-1.59)	
Prior heart failure hospitalization	Yes	None	96/350	Reference	0.18
		Mild	172/543	1.29 (0.97-1.71)	
		Moderate	115/322	1.27 (0.92-1.74)	
		Severe	46/101	1.72 (1.13-2.62)	
	No	None	146/836	Reference	
		Mild	215/972	1.13 (0.89-1.43)	
		Moderate	123/444	1.42 (1.08-1.87)	
		Severe	27/113	1.02 (0.64-1.63)	
Atrial fibrillation/flutter	Yes	None	59/290	Reference	0.97
		Mild	155/676	1.28 (0.91-1.80)	
		Moderate	143/438	1.45 (1.02-2.06)	
		Severe	51/152	1.42 (0.92-2.19)	
	No	None	187/915	Reference	
		Mild	238/861	1.18 (0.95-1.46)	
		Moderate	98/338	1.26 (0.96-1.65)	
		Severe	23/65	1.33 (0.80-2.22)	
LVEF	<50%	None	154/754	Reference	0.73
		Mild	228/868	1.24 (0.98-1.56)	
		Moderate	117/395	1.25 (0.95-1.65)	
		Severe	36/98	1.51 (0.99-2.29)	
	≥50%	None	92/446	Reference	
		Mild	164/667	1.12 (0.83-1.50)	
		Moderate	122/377	1.28 (0.93-1.77)	
		Severe	37/118	1.15 (0.73-1.81)	
Presence of intracardiac device	Yes	None	12/58	Reference	0.75
		Mild	48/160	1.72 (0.83-3.55)	
		Moderate	37/106	1.62 (0.75-3.49)	
		Severe	17/37	1.27 (0.49-3.31)	
	No	None	234/1147	Reference	
		Mild	345/1377	1.16 (0.96-1.39)	
		Moderate	204/670	1.28 (1.03-1.60)	
		Severe	57/180	1.33 (0.96-1.85)	
PASP	≥50mmHg	None	9/34	Reference	0.22
		Mild	49/181	0.72 (0.33-1.59)	
		Moderate	76/263	0.70 (0.32-1.52)	
		Severe	36/113	0.81 (0.35-1.85)	
	<50mmHg	None	124/598	Reference	
		Mild	282/1154	1.21 (0.96-1.53)	
		Moderate	138/430	1.45 (1.10-1.92)	
		Severe	31/93	1.38 (0.88-2.14)	
Moderate/Severe MR	Yes	None	51/202	Reference	0.12
		Mild	122/479	1.01 (0.70-1.46)	
		Moderate	138/445	1.16 (0.80-1.69)	
		Severe	36/127	1.02 (0.61-1.69)	
	No	None	192/992	Reference	
		Mild	266/1047	1.22 (0.99-1.51)	
		Moderate	101/325	1.44 (1.09-1.90)	
		Severe	38/88	1.88 (1.27-2.80)	
Moderate/Severe AS	Yes	None	19/63	Reference	0.65
		Mild	48/109	1.61 (0.79-3.24)	
		Moderate	23/58	1.62 (0.69-3.83)	
		Severe	6/15	0.98 (0.29-3.35)	
	No	None	224/1134	Reference	
		Mild	343/1416	1.16 (0.96-1.40)	
		Moderate	212/702	1.29 (1.04-1.61)	
		Severe	68/201	1.36 (0.99-1.86)	



classification for TR aetiology could not be adopted.[28] Since the echocardiographic parameters to evaluate diastolic function such as E/e' and left atrial volume were unavailable, our definition of isolated TR could include secondary TR due to HF with preserved ejection fraction. Further research is warranted to differentiate isolated TR from secondary TR due to HF with preserved ejection fraction. Third, the present study did not assess those echocardiographic parameters reflecting right ventricular dysfunction such as tricuspid annular plane systolic excursion, tricuspid valve systolic annular velocity, and fractional area change, which might be important to determine the indication for surgery.[3,4] Also, right ventricular-pulmonary arterial coupling was reported to be an important predictor for mortality in patients with secondary TR.[29] Fourth, TTE was not followed systemically after discharge and the number of patients with echocardiographic data at the 6 month visit available was limited, although the severity of TR could often improve or exacerbate depending on the volume status. Fifth, recent advances in HF medications including an angiotensin receptor-neprilysin inhibitor and sodium-glucose transport protein-2 inhibitors were not reflected at the enrolling period of the present study (2014–2016).

In conclusion, the grades of TR could successfully stratify the risk of all-cause death in a large Japanese AHF population. However, the association of TR with mortality was only modest and attenuated in patients aged 80 or more. Further research is warranted to evaluate how to follow up and manage TR in this elderly population.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Aetiology of tricuspid regurgitation.
Table S2. The detailed information about patients with moderate/severe tricuspid regurgitation who underwent tricuspid valve surgery.
Table S3. Clinical outcomes among 2807 patients who underwent TTE within 7 days after admission.
Figure S1. The transition of TR severity between the initial hospitalization and the 6-month visit.
Figure S2. The cumulative 1-year incidence according to the aetiology of TR.

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