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Original Article

Prevalence and predictive factors for clinical outcomes of isolated functional tricuspid regurgitation

Shoko Nakagawa (MD) [a,b], Hiroyuki Takahama (MD, PhD, FJCC) [a,c,*], Keiji Hoshino (MD) [a], Yoshiki Yanagi (MD) [d], Yuki Irie (MD) [a], Kenji Moriuchi (MD) [a], Masashi Amano (MD, PhD) [a], Atsushi Okada (MD, PhD) [a], Makoto Amaki (MD, PhD) [a], Hideaki Kanzaki (MD, PhD, FJCC) [a], Kengo Kusano (MD, PhD, FJCC) [a,b], Teruo Noguchi (MD, PhD) [a,b], Satoshi Yasuda (MD, PhD, FJCC) [a,c], Chisato Izumi (MD, PhD, FJCC) [a]

[a] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
[b] Department of Advanced Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[c] Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[d] Department of Clinical Physiology, National Cerebral and Cardiovascular Center, Suita, Japan

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A B S T R A C T

Background: A substantial number of patients have functional tricuspid regurgitation (TR).
Isolated functional TR has been undertreated and may be a next target for transcatheter intervention. However, the prevalence, patient characteristics, and predictive factors for prognosis remain unclear.
Methods: From patients in our echocardiographic database ($N = 64{,}242$), we extracted those with severe TR and examined prognosis according to etiologies of TR. Thereafter, we focused on two types of isolated functional TR; progressive TR after left-sided valve surgery (postoperative TR) and TR associated with annular dilatation (atrial TR). Composite adverse events were defined as all-cause death or hospitalization for heart failure (HF).
Results: Of 1001 patients with severe TR (median age, 77 years; female, 58 %), 71 (7 %) patients were classified as postoperative TR, and 149 (15 %) as atrial TR. During the follow-up period (median, 1.6 years), 30 composite adverse events were observed (postoperative TR, $n = 14$; atrial TR, $n = 16$). Composite adverse events were less frequent in these two types of functional TR than TR of other etiologies. Multivariate analysis adjusted for age and sex showed that a history of hospitalization for HF, history of cardiac surgery >2 times, loop diuretics, estimated glomerular filtration rate, blood urea nitrogen, hemoglobin, platelet level, left ventricular ejection fraction, and right ventricular dimension were associated with clinical adverse events ($p < 0.05$), while B-type natriuretic peptide level was not.
Conclusions: A considerable number of patients had isolated functional TR. Extracardiac factors such as renal function, hemoglobin and platelet are important in determining clinical outcomes.

Introduction

Tricuspid regurgitation (TR) is a heterogeneous condition that is observed in various cardiac diseases, and moderate to severe TR was reported to be associated with a poor outcome [1–3]. Generally, TR is classified as valvular (primary) or functional (secondary), and the latter type accounts for approximately 80 % of cases [4]. Functional TR commonly occurs as a result of left heart failure (HF) or pulmonary hypertension (PH) or both, but functional TR with no significant left HF or PH, is often seen in clinical settings [5–7]. As shown in 2020 Guidelines on the Management of Valvular Heart Disease in Japan [8], two representative etiologies of development of isolated functional TR have been suggested; progressive TR after left-sided valve surgery despite no significant left-sided valve dysfunction (postoperative TR) [9,10] and TR associated with tricuspid annular dilatation, which is usually coexistent with chronic atrial fibrillation (AF) (atrial TR) [5,11], and patients with these two types of isolated functional TR might be considered as candidates for isolated tricuspid valve (TV) intervention. However, the prevalence and determinants of clinical outcomes in these two types of functional TR remain uncertain. Therefore, no clear consensus exists for determining the optimal timing of surgery for these patients. On the other hand, these two types of isolated functional

* Corresponding author at: Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shinmachi, Suita, Osaka 564-8565, Japan.
E-mail address: hiroytakahama@gmail.com (H. Takahama).

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TR have been undertreated because of the high mortality of isolated TV surgery [12,13]. Recently, transcatheter intervention has been widely used in patients with aortic stenosis and mitral regurgitation, and these two types of isolated functional TR might be considered as the next target for transcatheter intervention in patients with high risk for surgery [14,15]. Therefore, clarifying the prevalence and predictive factors for prognosis in patients with these two types of isolated functional TR is important. Thus, this study aimed to investigate the prevalence, characteristics, and prognostic factors of these two types of isolated functional TR.

Methods

Study design

This was a retrospective study of patients who underwent transthoracic echocardiographic examination at the National Cerebral and Cardiovascular Center in Japan.

Patient population

We retrospectively analyzed our echocardiographic database and the medical records of consecutive patients ($N = 64{,}242$) who underwent echocardiography between January 2015 and December 2017 and identified 1116 (1.7 %) patients with severe TR. Twenty-nine patients who had an implanted left ventricular (LV) assist device or who underwent heart transplant were excluded from the study, as were 86 patients who did not undergo blood testing within 3 months of the echocardiographic examination. Thus, the remaining 1001 patients were enrolled in the study. We defined the main etiology of severe TR on the basis of clinical and echocardiographic findings and by referring to previous literature [4–6,10]. The diagnostic process for isolated functional TR in this study is shown as a flowchart (Fig. 1). As the first step, both congenital TR (any congenital heart disease resulting in TR) and primary TR (TR associated with structural tricuspid disease or a pacemaker/implantable cardioverter-defibrillator lead) were excluded. Among the remaining patients, i.e. those with functional TR, those with either functional TR with left-sided valve disease (mitral and/or aortic valve stenosis and/or regurgitation of at least moderate degree, or dysfunction of a left-sided valve prosthesis) or with LV ejection fraction (LVEF) < 40 % were excluded. Then, from the remaining patients, i.e. those with functional TR with normal left-sided valvular function and with LVEF ≥ 40 %, we excluded patients with right ventricular (RV) disease (arrhythmogenic RV cardiomyopathy or RV infarction) or PH (systolic pulmonary pressure ≥ 50 mmHg irrespective of whether it was post-capillary PH, pre-capillary PH, or of unspecified cause). Finally, the remaining patients, isolated functional TR, were classified into those with progressive TR after left-sided valve surgery despite no significant left-sided valve dysfunction (postoperative TR) and the remaining patients with severe TR (atrial TR), which was associated with annular dilatation. In our study, these two types of isolated functional TR patients which might be considered as the next target for transcatheter intervention were selected and patients with severe TR caused by RV dilation and tethering of the TV leaflets were excluded from isolated functional TR.

Echocardiographic measurements

Standard parameters were measured in accordance with the recommendations of the American Society of Echocardiography [16]. The presence and grade of TR were visually assessed by qualitative and semiquantitative methods, as previously described [17].

Estimated pulmonary artery systolic pressure was assessed by the maximal velocity of the TR jet using a modified version of Bernoulli's equation, as previously described [18]. Right atrial pressure was estimated by inferior vena cava diameter and the presence of inspiratory collapse according to the guideline [19]. RV dimension was determined from the RV mid-cavity linear dimension from the apical 4-chamber view, and RV end-diastolic dimension (RVEDD) was measured from stored images by experienced investigators in a blinded manner.

Laboratory measurements

All biochemical analyses were performed as routine clinical examinations. Estimated glomerular filtration rate (eGFR) was calculated as ml/min/1.73 m^2 with the formula $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ (×0.739 in women) [20]. Hepatorenal interaction was assessed with the Model of End-Stage Liver Dysfunction (MELD) score, which describes the function of these two organs. The score is calculated on the basis of creatinine and bilirubin values and was originally developed to assess the prognosis of patients with advanced liver disease [21]. The original MELD formula uses international normalized ratio (INR) values for risk stratification, so it cannot be used in patients receiving vitamin K antagonists (oral anticoagulants). Therefore, in our study population, we used a modified MELD formula that excludes INR value (MELD-XI), as follows: $[5.11 \times \log \text{bilirubin (mg/dl)}] + [11.76 \times \log \text{creatinine (mg/dl)}] + 9.44$ [21]. In accordance with the recommendations of the United Network for Organ Sharing for liver transplant organ allocation in the USA and other authors, the lower limits of bilirubin and creatinine were each set at 1.0 mg/dl [21]. In calculating the MELD-XI score for this analysis, values of bilirubin and creatinine <1.0 mg/dl were assigned a value of 1.0 mg/dl. The cut-offs for abnormal values were set at >1.0 mg/dl for both serum creatinine and total bilirubin levels.

Clinical outcomes

For two years after the date of the echocardiographic examination, we investigated all causes of death and hospitalization for HF by reviewing the medical charts. The primary endpoint was a composite of all-cause death and hospitalization for HF.

Ethics

This study was performed according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee (approval number: M30-059). It was designed to be performed without obtaining individual informed consent, according to the “opt-out” principle. Instead, we publicized a summary of the study protocol with the contact information for our office on the institution website, which enabled patients to refuse enrollment in the study.

Statistical analysis

Values are expressed as the median and interquartile range (IQR). Categorical data were compared between groups using chi-squared test, and continuous values were compared using Wilcoxon test. All tests were two sided, and $p < 0.05$ was considered statistically significant. Prognostic predictors were evaluated by Kaplan-Meier analysis using the log-rank test and Cox regression hazard analysis. All statistical analyses were performed using JMP 12 (SAS Institute, Inc., Cary, NC, USA).

Results

Overall TR patient characteristics and outcomes

Fig. 1 summarizes the prevalence of TR of each etiology. Among the 1001 enrolled patients with severe TR, 139 had primary TR and 748 had secondary (functional) TR. Postoperative TR was observed in 71 (7 % of overall enrolled patients), and they had experienced previous left-sided valve surgery (mitral valve surgery, $n = 21$; aortic valve surgery, $n = 29$; combined aortic and mitral valve surgery, n = 21), but no left-

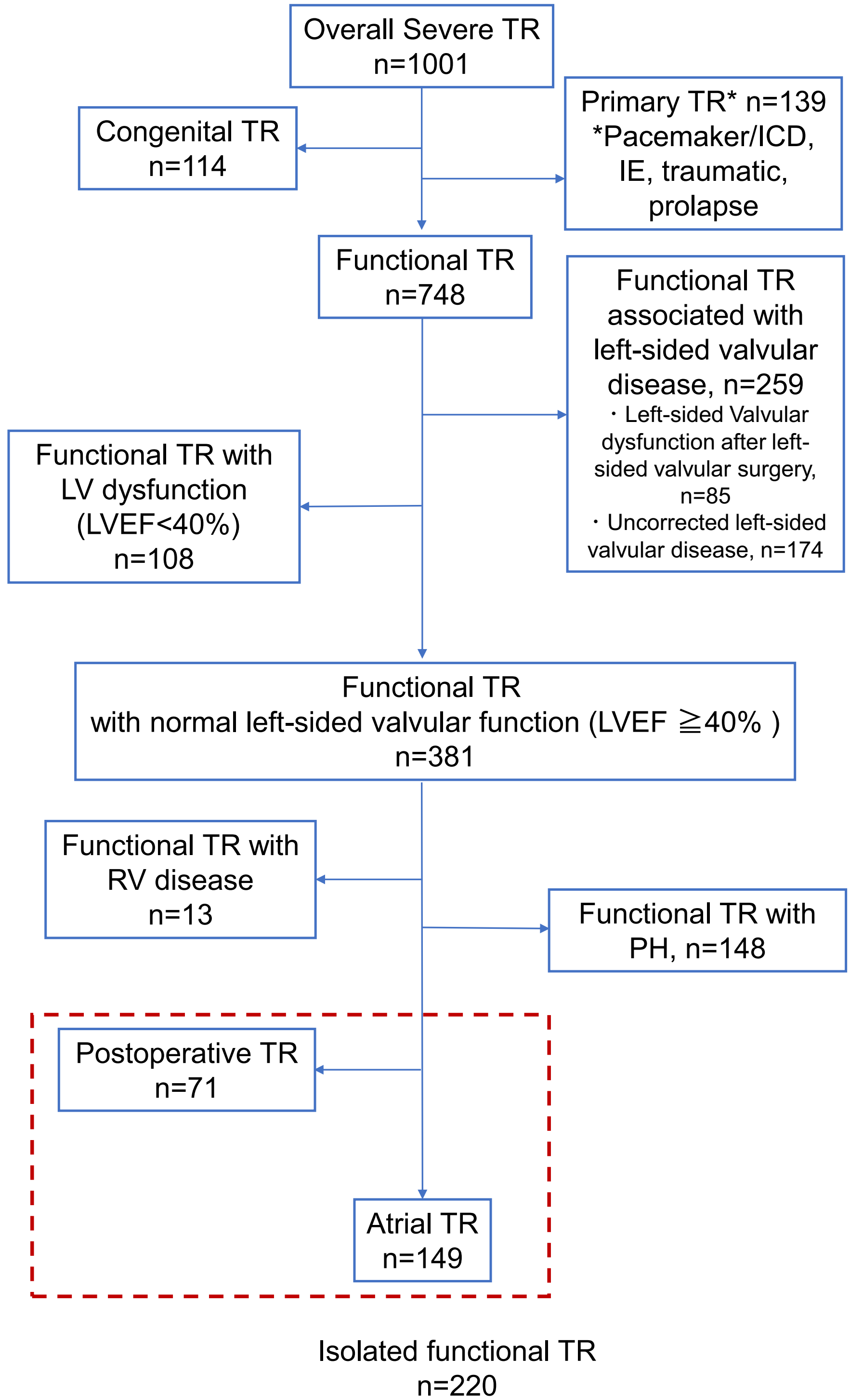

Fig. 1. Diagnostic flowchart of etiology of TR. Diagnostic process for enrolled severe TR patients who underwent echocardiography between January 2015 and December 2017. Among 1001 patients with severe TR, 220 patients were classified as isolated functional TR.
TR, tricuspid regurgitation; IE, infective endocarditis; ICD, implantable cardioverter-defibrillator; LV, left ventricle; LVEF, left ventricular ejection fraction; RV, right ventricle; PH, pulmonary hypertension.

sided valve dysfunction. Atrial TR was observed in 149 patients (15 % of overall); thus, isolated functional TR was observed in 220 patients (22 % of overall).

The characteristics of all patients with severe TR are summarized in Table 1. The total cohort comprised 422 men and 579 women, with a median age of 77 years. Approximately one-third (34 %) of patients had a history of hospitalization for HF, and the median LVEF was 58 % (IQR, 49–63 %). The study participants were characterized by low eGFR (median, 52 ml/min/1.73 m^2) and elevated plasma level of B-type natriuretic peptide (BNP; median, 208 pg/ml). Forty four percent of patients received loop diuretics.

During the follow-up period (median, 1.6 years), the composite of adverse events occurred in 214 of all patients with severe TR (all causes of death, $n = 85$; hospitalization for HF, $n = 158$, median interval after index echocardiographic study: 223 days). Seventy-four (7 %) patients underwent TV surgery (median interval after index echocardiographic

Table 1
Baseline patient characteristics.

	Overall	Isolated functional TR	Postoperative TR	Atrial TR	*p*-Value[a]
Patient number	1001	220	71	149	
Age (years)	77 (69–83)	79 (73–84)	80 (75–85)	76 (71–83)	0.002
Gender (male %)	422 (42)	96 (44)	21 (30)	75 (50)	0.003
NYHA class					0.063
Class III, N (%)	348 (35)	37 (17)	11 (15)	26 (17)	
Class IV, N (%)	43 (4)	5 (2)	3 (4)	2 (1)	
History of hospitalization for HF, N (%)	341 (34)	52 (24)	26 (37)	26 (17)	0.002
Hypertension, N (%)	427 (47)	114 (56)	27 (40)	87 (64)	0.001
DM, N (%)	179 (20)	46 (23)	13 (19)	33 (24)	0.432
Dyslipidemia, N (%)	260 (38)	68 (34)	22 (33)	46 (34)	0.888
AF, N (%)	470 (48)	159 (75)	37 (54)	122 (84)	<0.001
Echocardiography					
LVEDD (mm)	47 (42–52)	45 (41–50)	45 (41–50)	46 (41–50)	0.585
LVESD (mm)	31 (27–37)	30 (26–33)	30 (26–34)	30 (27–33)	0.712
LVEF (%)	58 (49–63)	63 (56–63)	63 (57–63)	63 (56–63)	0.576
RVEDD (mm)	36 (31–42)	35 (31–40)	37 (32–41)	35 (31–40)	0.087
LAVI (ml/m^2)	71 (49–103)	72 (53–94)	83 (60–103)	67 (52–91)	0.019
TRPG (mmHg)	33 (26–43)	28 (24–32)	27 (24–31)	28 (24–33)	0.490
Estimated RAP (mmHg)	8 (3–8)	3 (3–8)	8 (3–8)	3 (3–8)	0.037
Estimated PASP (mmHg)	40 (31–52)	34 (28–40)	35 (29–41)	33 (28–40)	0.354
Laboratory data					
eGFR (ml/min/1.73 m^2)	52 (38–64)	53 (40–65)	51 (40–64)	54 (42–65)	0.866
BUN (mg/dl)	20 (16–27)	20 (15–25)	20 (16–24)	20 (15–27)	0.946
Total bilirubin (mg/dl)	0.7 (0.6–1.0)	0.7 (0.6–1.0)	0.8 (0.6–1.0)	0.7 (0.5–1.0)	0.180
AST (U/l)	27 (21–34)	26 (21–32)	29 (24–36)	26 (21—31)	0.007
ALT (U/l)	16 (12—23)	16 (13—22)	17 (14–23)	16 (12—21)	0.073
Hemoglobin (g/dl)	12.3 (10.9–13.5)	12.6 (11.1–13.7)	12.3 (10.5–13.3)	12.7 (11.4–13.9)	0.023
PLT ($\times 10^3$/μl)	156 (119–190)	157 (123–186)	150 (116–176)	158 (131–190)	0.076
BNP (pg/ml)	208 (98–407)	169 (87–278)	114 (71–226)	190 (101–292)	<0.001
MELD-XI	9.9 (9.4–12.7)	9.9 (9.4–12.5)	9.9 (9.4–12.5)	9.9 (9.4–12.6)	0.943
Medications					
ACE-I or ARB, N (%)	292 (30)	75 (36)	16 (23)	59 (42)	0.006
Beta blockers, N (%)	233 (24)	61 (29)	17 (24)	44 (31)	0.292
Loop diuretics, N (%)	521 (44)	91 (43)	41 (59)	50 (35)	0.001
MRA, N (%)	232 (24)	50 (24)	23 (33)	27 (19)	0.030
Warfarin, N (%)	440 (46)	106 (50)	48 (69)	58 (41)	<0.001
DOAC, N (%)	174 (18)	48 (23)	2 (3)	46 (33)	<0.001
Outcomes					
All cause death-(1)	85 (8)	9 (4)	4 (6)	5 (3)	0.437
Cardiovascular death	30 (30)	2 (0.9)	2 (3)	0 (0)	0.033
Hospitalization for HF-(2)	158 (16)	23 (11)	11 (15)	12 (8)	0.101
Composite of (1) and (2)	219 (22)	30 (14)	14 (20)	16 (11)	0.077
TV surgery	74 (7)	3 (1)	1 (1)	2 (1)	0.969

The baseline characteristics of all study patients and isolated functional TR are shown. Comparison between the two types of isolated functional TR is also shown. Continuous values are expressed as median with interquartile range (median [25th percentile, 75th percentile]).
TR, tricuspid regurgitation; NYHA, New York Heart Association; HF, heart failure; DM, diabetes mellitus; AF, atrial fibrillation; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; RVEDD, right ventricular end-diastolic dimension; LAVI, left atrial volume index; TRPG, tricuspid regurgitation pressure gradient; RAP, right atrial pressure; PASP, pulmonary artery systolic pressure; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; PLT, platelet; BNP, B-type natriuretic peptide; MELD, the Model of End-Stage Liver Dysfunction; MELD-XI, MELD excluding INR (international normalized ratio); ACE—I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; DOAC, direct oral anticoagulant; TV, tricuspid valve.
[a] Comparison between postoperative TR and atrial TR.

study: 102 days). Of 74 patients, only 4 patients underwent isolated TV surgery and remaining patients underwent TV surgery with left-sided valve surgery or congenital heart disease surgery.

Characteristics and outcomes of patients with postoperative TR and atrial TR

The baseline characteristics of patients with postoperative TR and atrial TR are also shown in Table 1. In postoperative TR, the median time between echocardiographic examination and the previous operation was as follows: mitral valve surgery, 14.3 years (IQR, 10.3–27.4 years); aortic valve surgery, 5.1 years (IQR, 2.1–12.2 years); and combined valve surgery, 19.2 years (IQR, 9.4–23.1 years). A history of hospitalization for HF was more common in patients with postoperative TR, and hypertension was more frequently observed in patients with atrial TR. Thirty-eight patients with postoperative TR represented AF (54 % of postoperative TR group), and 122 patients with atrial TR had AF (84 % of atrial TR group). Patients with postoperative TR were younger than those with atrial TR and had a larger left atrial volume index. Other echocardiographic parameters, including RVEDD, showed no significant differences. Regarding laboratory data, patients with postoperative TR had lower hemoglobin and plasma BNP levels than those with atrial TR. We found no difference in eGFR or blood urea nitrogen (BUN). Treatment with loop diuretics and mineralocorticoid receptor antagonists was more common in patients with postoperative TR than in those with atrial TR. A total of 30 composite adverse events occurred (atrial TR, $n = 16$; postoperative TR, $n = 14$), 23 of which were hospitalization for HF. All cause death occurred in 9 patients; cardiac death in only 2 patients, non-cardiac death in 4 patients (liver dysfunction, gastrointestinal hemorrhage, septic shock, and intestinal obstruction in 1 patient, respectively), and the causes of death were unknown in 3 patients. Three patients underwent TV surgery.

Predictive factors for clinical outcome in patients with isolated functional TR

Clinical composite adverse events were significantly less frequent in these two types of isolated functional TR than in other etiologies, as shown in Fig. 2. We found no difference in composite adverse events between postoperative TR and atrial TR (20 % vs. 11 % at two

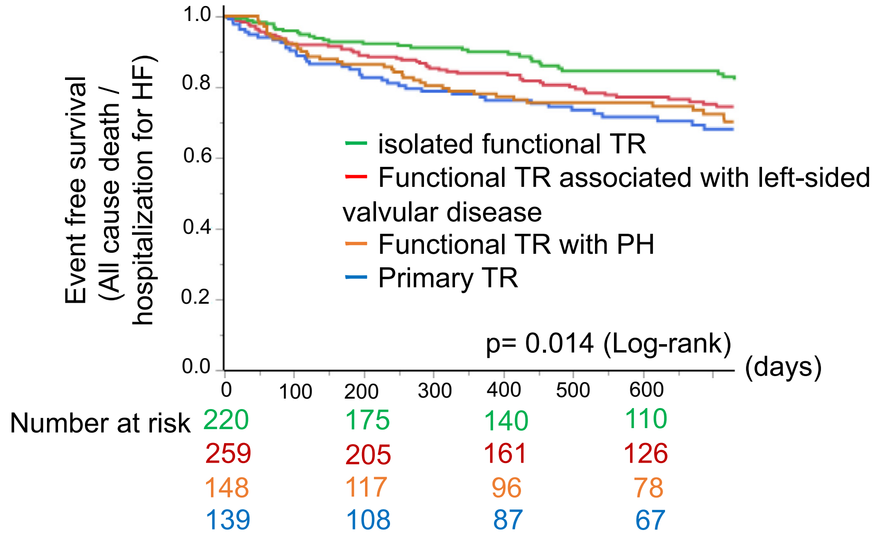

Fig. 2. Clinical outcomes in patients with TR of each etiology. Kaplan-Meier curves for the composite of adverse events in patients with TR of each etiology (red line, functional TR with left-sided valvular disease; orange line, functional TR with pulmonary hypertension; blue line, primary TR; and green line, isolated functional TR).
TR, tricuspid regurgitation; PH, pulmonary hypertension; HF, heart failure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

years, $p = 0.094$; Fig. 3), even though the group of patients with atrial TR included more older patients than the group with postoperative TR. Table 2 shows Cox proportional hazard models for the composite adverse events in patients with the two types of isolated functional TR. In this table, the "adjusted HR" model was adjusted by age and sex. History of hospitalization for HF, history of cardiac surgery >2 times, loop diuretics, LVEF, RVEDD, eGFR, BUN, hemoglobin, and platelet levels were associated with clinical adverse events ($p < 0.05$). Fig. 4 shows the Kaplan-Meier curves stratified by history of hospitalization for HF, BNP, eGFR, and hemoglobin level. Cumulative event-free survival was not significantly different regardless of the BNP level.

Discussion

We investigated patients with severe TR by focusing on functional TR, which is considered the next target of transcatheter intervention. Our main results were as follows: 1) Among consecutive patients who underwent echocardiography ($n = 64{,}242$), we identified severe TR in about 2 %; in these patients, isolated functional TR which might be considered as candidates for isolated TV intervention, i.e. postoperative TR and atrial TR, accounted for approximately 20 % of cases, 2) patients with these two types of isolated functional TR had a better outcome than those with other etiologies, 3) extracardiac factors such as renal function, hemoglobin, and platelets were as important as cardiac factors in predicting clinical outcome in patients with these two types of isolated functional TR.

Prevalence and clinical background of isolated functional TR

The prevalence of isolated functional TR identified in our study was 22 %. Topilsky et al. estimated the prevalence and distribution patterns of significant TR, and it was reported that 8 % of patients with severe TR had isolated TR. Postoperative TR (progressive TR occurring in

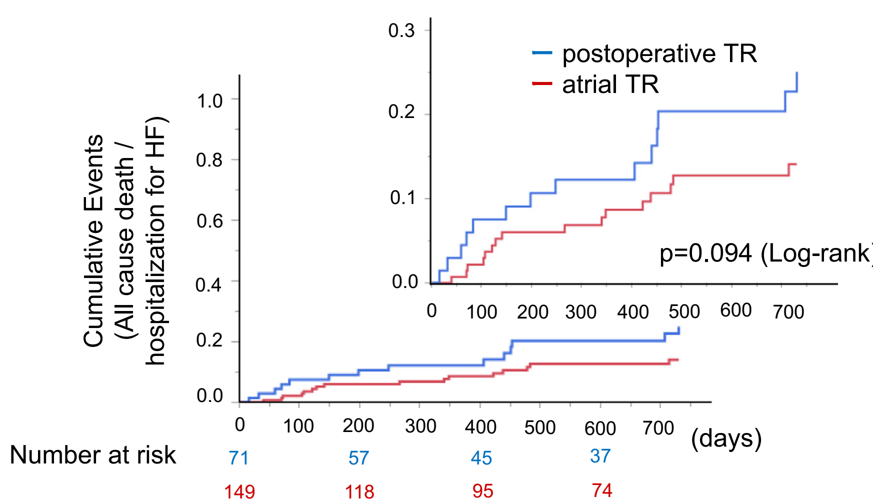

Fig. 3. Clinical outcomes in patients with postoperative TR and atrial TR. Kaplan-Meier curves for the composite of adverse events in patients with postoperative TR and atrial TR (blue line, postoperative TR; red line, atrial TR).
TR, tricuspid regurgitation; HF, heart failure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Cox proportional hazards model for occurrence of composite adverse events in patients with isolated functional TR.

	Isolated functional TR (n = 220)			
	Unadjusted HR (95%CI)	p-Value	Adjusted HR (95 % CI) (Adjusted model)	p-Value
History of hospitalization for HF	2.673 (1.272–5.484)	0.010	2.912 (1.368–6.058)	0.006
History of cardiac surgery >2 times	3.365 (1.123–8.263)	0.032	3.456 (1.140–8.637)	0.031
Atrial TR	0.546 (0.266–1.135)	0.103		
Loop diuretics	2.608 (1.249–5.811)	0.010	2.606 (1.246–5.816)	0.011
LVEDD, 1 mm	1.021 (0.967–1.085)	0.480		
LVEF, 1 %	0.943 (0.902–0.989)	0.017	0.931 (0.887–0.980)	0.007
LAVI, 1 ml/m^2	1.001 (0.994–1.004)	0.773		
RVEDD, 1 mm	1.067 (1.017–1.117)	0.009	1.080 (1.028–1.131)	0.003
TRPG, 1 mmHg	1.026 (0.955–1.099)	0.482		
Estimated RAP, 1 mmHg	0.992 (0.911–1.071)	0.840		
Estimated PASP, 1 mmHg	0.969 (0.929–1.015)	0.179		
Total bilirubin, 0.1 mg/dl	1.020 (0.935–1.094)	0.630		
AST, 1 U/l	0.992 (0.957–1.013)	0.518		
ALT, 1 U/l	0.997 (0.963–1.019)	0.836		
Log BNP	1.322 (0.864–1.989)	0.196		
eGFR, 1 ml/min/1.73 m^2	0.932 (0.910–0.954)	<0.001	0.933 (0.910–0.954)	<0.001
BUN, 1 mg/dl	1.042 (1.027–1.054)	<0.001	1.045 (1.029–1.059)	<0.001
Hemoglobin, 1 g/dl	0.658 (0.545–0.795)	<0.001	0.644 (0.529–0.785)	<0.001
PLT, 10^4/μl	0.863 (0.785–0.944)	<0.001	0.844 (0.764–0.927)	<0.001
MELD-XI Score, 1 point	1.009 (0.934–1.068)	0.793		

The "adjusted HR" model was adjusted by age and sex.
TR, tricuspid regurgitation; HR, hazard ration; CI, confidence interval; NYHA, New York Heart Association; HF, heart failure; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; RVEDD, right ventricular end-diastolic dimension; TRPG, tricuspid regurgitation pressure gradient; RAP, right atrial pressure; PASP, pulmonary artery systolic pressure; AST, aspartate transaminase; ALT, alanine transaminase; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; PLT, platelet; MELD, the Model of End-Stage Liver Dysfunction; MELD-XI, MELD excluding INR (international normalized ratio).

patients after left-sided valve prosthesis or repair without significant left-sided valve dysfunction) was not mentioned in this study [4]. The prevalence of even only atrial TR identified in our study was 15 %, which was higher than that reported by Topilsky et al. [4]. Takahashi et al. reported that the prevalence of atrial TR was 21 % in Japanese severe TR patients [11], which was compatible with the results of our study. The enrolled patients with atrial TR in our study were older (median: 80 years) than those in previous studies from the USA [4–6]. The high prevalence of atrial TR associated with AF may reflect the aging society of Japan.

Patients with postoperative TR had a large left atrial volume, frequent history of hospitalization for HF, and high frequency of

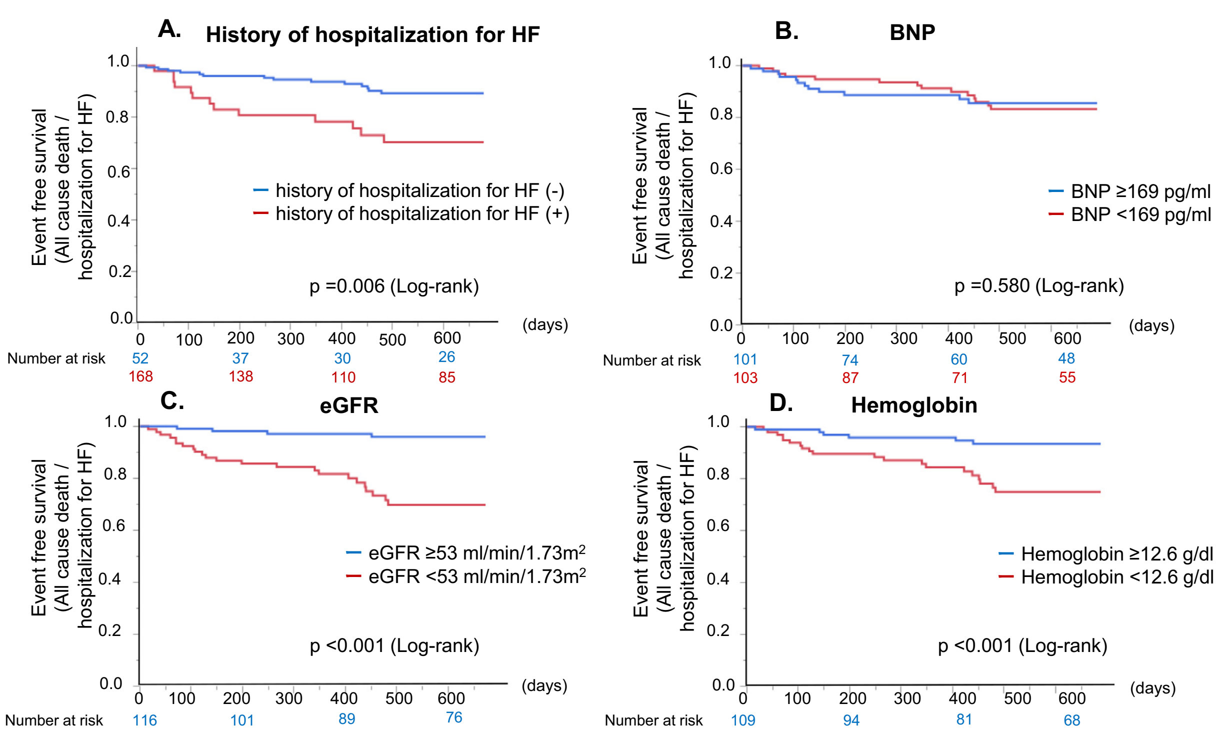

Fig. 4. Kaplan-Meier curves for the composite of adverse events stratified by associated factors. Kaplan-Meier curves stratified by history of hospitalization for HF (A), BNP (B), eGFR (C), and hemoglobin levels (D).
HF, heart failure; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

medication use. The old age of patients with atrial TR and the high surgical risk in those with postoperative TR may increase the mortality with isolated TV surgery, which may explain why this type of surgery has been performed in a relatively small number of patients.

Prognosis of isolated functional TR and its predictive factors for clinical outcomes

In this study, substantial differences in clinical outcomes according to the etiology for TR were observed as shown in Fig. 2. These findings raise the possibility that etiology of severe TR is associated with the clinical outcomes. In other words, the severity of underlying cardiac disease (cardiac damage or hemodynamic disorder) is associated with the clinical outcome. Notably, a more favorable outcome was observed in patients with isolated functional TR compared with those with TR of other etiologies. The cumulative event rate at 2 years after the date of echocardiographic examination was 14 % in patients with isolated functional TR.

A history of hospitalization for HF itself was a strong predictive factor of worse clinical outcome. Other significant determinants were extracardiac factors, i.e. renal factors (represented by eGFR and BUN levels), low hemoglobin level (anemia), and platelet count. In contrast, plasma BNP level was not associated with clinical outcome. In patients with isolated functional TR, right-sided heart failure is the main clinical picture, extracardiac factors as a marker of systemic organ congestion may be important prognostic determinants, rather than BNP.

In addition, severe TR promotes chronic volume overload to RV, which leads to progressive RV dilation. Indeed, larger RVEDD was a significant prognostic predictor as shown in Table 2. A previous study reported that RV enlargement was an important pathological mechanism for the development of significant TR in chronic AF patients [22]. Another study suggested that RV end-systolic area was an independent predictor of postoperative outcome in patients with isolated severe TR [23]. However, due to the complex geometry of the RV, RVEDD is not sufficient to evaluate RV volume. Accurate evaluation of RV volume by routine echocardiography is still difficult, and further investigation is necessary.

Renal function and anemia as prognostic predictors of TR

In accordance with previous studies [24–26], this study showed that renal function is a key predictor of clinical outcome in patients with isolated functional TR, even compared with the function of other organs such as the liver. Indeed, several previous studies have already showed that elevated central venous pressure may result in impaired renal perfusion and dysfunction, leading to poorer clinical outcomes in patients with HF [27,28]. Such a cascade may be considered as one of the mechanisms of disease progression in TR.

Low hemoglobin level was also associated with worse clinical outcomes. Anemia has been well known as an independent prognostic predictor in HF patients with reduced or preserved ejection fraction [29,30]. In severe TR patients, renal perfusion is decreased, or renal congestion occurs, which also leads anemia. In addition, hypersplenism may affect anemia because of long-standing systemic venous congestion due to volume overload to RV, right atrium, and subsequently portal vein and splenic vein [23]. It is worth considering that the interplay among renal dysfunction, hypersplenism, and anemia are associated with clinical outcomes in patients with severe TR. A previous report suggested a preoperative hemoglobin cut-off of 11.3 g/dL for predicting event-free survival in severe TR [23].

Future direction

Although a relatively favorable prognosis was found in this study, patients who experienced HF hospitalization showed a high risk for adverse events. Patients with renal dysfunction, anemia, or thrombocytopenia also showed a high risk for adverse events. The guidelines mention isolated tricuspid valve surgery for functional TR [8,31,32], but evidence is still limited. In the real world, physicians often face difficulty determining the surgical indications and their optimal timing. Indeed, despite the substantial number of patients with isolated functional TR who were hospitalized with HF during the follow-up period ($n = 23$), TV surgery was performed in only three patients in the present study. The relatively low rate of referral to a surgeon indicates that patients with severe TR with a high risk of HF are not treated by TV surgical intervention. Recently, a new risk score for in-hospital mortality prediction after isolated TV surgery was developed in France (TRI-SCORE) [33]. This risk score model relied on four clinical parameters (age, New York Heart Association functional class, right-sided heart failure signs, and daily dose of furosemide), two laboratory parameters (glomerular filtration rate and total bilirubin), and two echocardiographic parameters (LVEF and moderate/severe RV dysfunction). This risk score model predicted 1-year mortality with good accuracy. However, in that study, there are big differences regarding age (mean 60 years) and the rate of functional TR (49 %) compared with our study as well as the published cohorts from Japan [11]. Therefore, it seems hard for simple adaptation of TRI-SCORE to our population. The risk score for prognosis after isolated TV surgery applicable to Japanese should be developed and the new risk score could be useful in determining the optimal timing of isolated TV surgery in isolated functional TR patients.

In near future, TV transcatheter intervention could be utilized in patients with functional TR. Beneficial effects of TV transcatheter intervention for this population should be clarified.

Limitations

This study has several limitations. First, it was a retrospective study of routine echocardiographic studies, so available data of echocardiographic parameters were limited. For example, in the present study, larger RVEDD was associated with the clinical composite of adverse events. We only measured RV mid-cavity width and we have insufficient data on RV structure and function such as tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RV FAC), RV volume measured by three-dimensional method, or RV strain. Further investigation will be necessary to address this problem. Second, the study was cross-sectional and therefore included patients with multiple stages of severe TR, and the disease stage per se is associated with clinical outcome. Third, follow-up period was short and the number of events was relatively small, limiting the statistical power and the ability to perform multivariate analysis. Despite these limitations, this study is valuable because only limited evidence is available on two types of isolated functional TR. It shed light on the clinical features of two types of functional TR and showed the prognostic importance and substantial clinical significance of extracardiac factors other than TR stages in a considerable number of patients with severe TR. At our institution, we have been performing a prospective study on patients with severe TR (UMIN Clinical Trials Registry number 000034926) since 2018, and we hope that this project will provide data to complement the findings of this retrospective study.

Conclusions

This study found that a considerable number of patients with severe TR have isolated functional TR in Japan, reflecting this aging society. It also showed that extracardiac factors such as renal function, hemoglobin, and platelets are significant in determining clinical outcomes in these patients.

Declaration of competing interest

Makoto Amaki reports remuneration for lecture from Abbott. Chisato Izumi reports remuneration for lecture from Daiichi Sankyo, Otsuka Pharmaceutical, Edwards Lifesciences, Novartis Japan, and Boehringer Ingelheim. The other authors have nothing to disclose in connection with this article.

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