学位論文

Prognostic Predictors of Tricuspid Regurgitation Worsening after Mitral Regurgitation Surgery with Mild Tricuspid Regurgitation
（軽度三尖弁閉鎖不全症合併症例に対する僧帽弁閉鎖不全症手術後の三尖弁閉鎖不全症悪化の予後予測因子の検討）

羽田　佑

Tasuku　Hada

熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

指導教員

野口　暉夫　客員教授

熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

泉　知里　客員教授

熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

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著 者 名　：　羽田　佑
Tasuku Hada

指導教員名　：　熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学　野口 暉夫 客員教授
熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学　泉 知里 客員教授

審査委員名　：　心臓血管外科学担当教授　福井 寿啓
総合診療・臨床疫学担当教授　松井 邦彦
心臓発生学担当特任准教授　有馬 勇一郎

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Prognostic Predictors of Tricuspid Regurgitation Worsening after Mitral Regurgitation Surgery with Mild Tricuspid Regurgitation

Tasuku Hada, MD,[,†] Masashi Amano, MD, PhD,[*] Shunsuke Murata, PhD,[‡] Kunihiro Nishimura, MD, PhD,[‡] Shoko Nakagawa, MD,[*] Yuki Irie, MD,[*] Kenji Moriuchi, MD,[*] Atsushi Okada, MD, PhD,[*] Takeshi Kitai, MD, PhD,[*] Makoto Amaki, MD, PhD,[*] Hideaki Kanzaki, MD, PhD,[*] Satsuki Fukushima, MD, PhD,[$] Kengo Kusano, MD, PhD,[*,†] Teruo Noguchi, MD, PhD,[*,†] Tomoyuki Fujita, MD, PhD,[$] and Chisato Izumi, MD, PhD[*]*

We aimed to investigate the prevalence and predictors of postoperative tricuspid regurgitation (TR) worsening in patients with mitral regurgitation (MR) and concomitant ≤mild TR. A total of 620 patients underwent surgery for MR from 2013 to 2017. Of these, 260 had ≤mild preoperative TR and no concomitant tricuspid valve surgery and were enrolled in this single-center retrospective study. The primary endpoint was postoperative worsening of ≥moderate TR. The primary endpoint occurred in 28 of 260 patients (11%) during the follow-up period [median: 4.1 years (interquartile range: 2.9–6.1 years)]. In the multivariable analysis, age, female sex, and left atrial volume index (LAVI) were significant predictors of the primary outcome during intermediate-term follow-up (age: hazard ratio [HR] 1.05 per 1-year increment, 95% confidence interval [CI] 1.02–1.10, P = 0.003; female sex: HR 3.53, 95% CI 1.61–7.72, P = 0.002; LAVI: HR 1.17 per 10-mL/m^2 increment, 95% CI 1.07–1.26, P < 0.001). The optimal LAVI cut-off value for predicting postoperative TR worsening was 79 mL/m^2 (area under the curve: 0.69). A high LAVI (>79 mL/m^2) was significantly associated with a low rate of freedom from postoperative TR worsening compared with a low LAVI (≤79 mL/m^2) (82.6% vs 93.9% at 5 years, respectively; log-rank P = 0.008). In patients with ≤mild preoperative TR and no concomitant tricuspid surgery, the rate of postoperative TR worsening was 11% during intermediate-term follow-up. LA enlargement in patients with MR and ≤mild preoperative TR was significantly associated with postoperative TR worsening.

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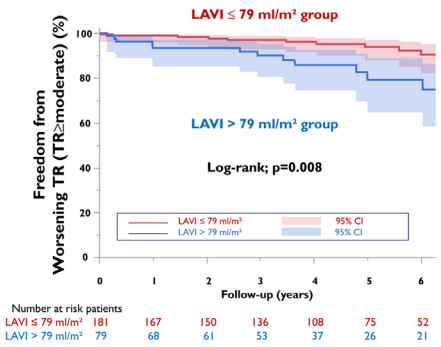

Clinical outcomes of left atrial volume index for tricuspid regurgitation worsening.

Central Message

Left atrial enlargement in patients with mitral regurgitation and mild preoperative tricuspid regurgitation (TR) was significantly associated with postoperative TR worsening.

Perspective Statement

The present study shows that preoperative left atrial (LA) volume is a useful surrogate marker to predict postoperative tricuspid regurgitation

Abbreviations: AF, atrial fibrillation; LAD, left atrial diameter; LAVI, left atrial volume index; MR, mitral regurgitation; TA, tricuspid annulus; TAD, tricuspid annulus diameter; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation pressure gradient

*Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
†Department of Advanced Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
‡Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
$Department of Cardiac Surgery, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

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Informed Consent Statement: This study was classified as a noninterventional study because it did not use invasive procedures or human-derived specimens; thus, the requirement for informed consent was waived. However, the details of the study were disseminated to patients and their families/caregivers, with the opportunity for patients to decline study participation (opt-out).

Address reprint requests to: Masashi Amano, MD, PhD, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan, Phone: +81-6-6170-1070, Fax: +81-6-6170-1782. E-mail: m.amano@ncvc.go.jp

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(TR) worsening in the clinical setting. A larger preoperative LA volume may be useful, suggesting that clinicians should pay attention to postoperative follow-up after surgery in patients with mitral regurgitation with mild preoperative TR.

INTRODUCTION

The prognosis of patients with progressive tricuspid regurgitation (TR) during long-term follow-up after left-sided valve surgery, especially surgery for mitral regurgitation (MR), is poor.[1-4] Atrial fibrillation (AF), tricuspid annulus (TA) dilatation, and right ventricular dysfunction have been reported as prognostic predictors in these patients.[2-6] Therefore, the current guidelines of American College of Cardiology (ACC) / American Heart Association (AHA) and European Society of Cardiology (ESC) for valvular heart diseases recommend the aggressive concomitant surgical intervention for significant TR with Class I (severe TR) or IIa (moderate TR with TA dilatation) when a left-sided valve surgery is performed.[7,8] However, these guidelines have not reached a consensus in terms of the usefulness of concomitant surgery for mild TR because of the limited evidence.

Specifically, concomitant surgery for mild TR is recommended for Class IIa in 2021 ESC guidelines and for Class IIb in 2020 JCS guidelines with TA dilation, while there are no recommendations in 2020 ACC/AHA guidelines.[7-9] A recent randomized controlled trial that investigated the necessity of concomitant tricuspid annuloplasty in patients with severe degenerative MR and ≤moderate TR reported that postoperative TR worsening occurred almost exclusively in patients with moderate preoperative TR, but not in those with ≤mild TR and TA dilatation. Thus, they called into question reliance on the measurement of the TA diameter (TAD) to decide whether to perform concomitant tricuspid valve surgery at the time of mitral valve surgery in patients with mild TR.[10] No studies have reported the prevalence and predictors of postoperative TR worsening after surgery for MR specifically in patients with ≤mild preoperative TR. The JCS recommendation is based on previous data demonstrating the relationship between persistent AF or TA dilatation and postoperative TR worsening.[4,11-13] On the other hand, whether AF contributes to worsening of postoperative TR, even after surgery for MR in the era of the Maze procedure for concomitant AF, remains unclear.[14] In current guidelines, the TA dilatation cut-off value for concomitant surgery on the tricuspid valve is a TA diameter (TAD) of >40 mm and/or a TAD index of >21 mm/m^2, as measured in the apical 4-chamber view on transthoracic echocardiography.[7-9] However, the data supporting the use of these values are limited,[15] and other studies have suggested that a TAD of >40 mm is not a predictor of postoperative TR worsening after mitral valve surgery.[16,17] Thus, the usefulness of a TAD of >40 mm and/or a TAD index of >21 mm/m^2 for predicting postoperative TR worsening is controversial, especially in patients with ≤mild preoperative TR.[18,19] To address this issue, we aimed to investigate the prevalence and predictors of postoperative TR worsening in patients with MR and concomitant ≤mild preoperative TR.

METHODS

Study Population

A total of 620 consecutive patients who underwent mitral valve surgery for MR from January 2013 to December 2017 were retrospectively enrolled. Patients who underwent previous open-heart surgery (n = 78) or with concomitant ≥moderate mitral stenosis (n = 51), active infective endocarditis (n = 23), pacemaker implantation (n = 20), systolic anterior motion of the mitral valve (n = 14), acute MR (n = 7), or concomitant congenital heart disease (n = 5) were excluded. Of the 422 remaining patients, 260 patients with ≤mild preoperative TR who did not undergo concomitant tricuspid valve surgery were enrolled (Figure 1). The demographic and baseline clinical data of the patients were collected just before surgery.

This study was approved by the institutional review board of the National Cerebral and Cardiovascular Center, Suita, Japan (R19095; approval number: 19-322; approval date: December 28, 2019). This study was classified as a noninterventional study because it did not use invasive procedures or human-derived specimens; thus, the requirement for informed consent was waived. However, the details of the study were disseminated to patients and their families/caregivers, with the opportunity for patients to decline study participation (opt-out).

Surgical Indication and Procedure

The surgical indications for MR were determined according to current guidelines, and all procedures were performed by experienced surgeons. A full median sternotomy or minimally invasive cardiac surgery was performed. Mitral valve replacement or mitral valve repair using an approved rigid or semi-rigid annuloplasty ring was performed according to the etiology and the degree of dysfunction. In patients with AF, a modified Cox maze procedure was performed using a cryoablator prior to mitral valve surgery, if indicated.[20] Concomitant coronary artery bypass grafting was also performed with the use of standard techniques.

Echocardiographic Evaluation and Clinical Outcome

Echocardiography data before surgery; at discharge following surgery; and at 1, 3, 5, and 7 years after surgery were analyzed. Two-dimensional echocardiography and Doppler imaging were performed in all patients in accordance with the guidelines of the American Society of Echocardiography.[21-24] Left atrial (LA) volume was calculated using the biplane modified Simpson method and indexed to body surface area. MR

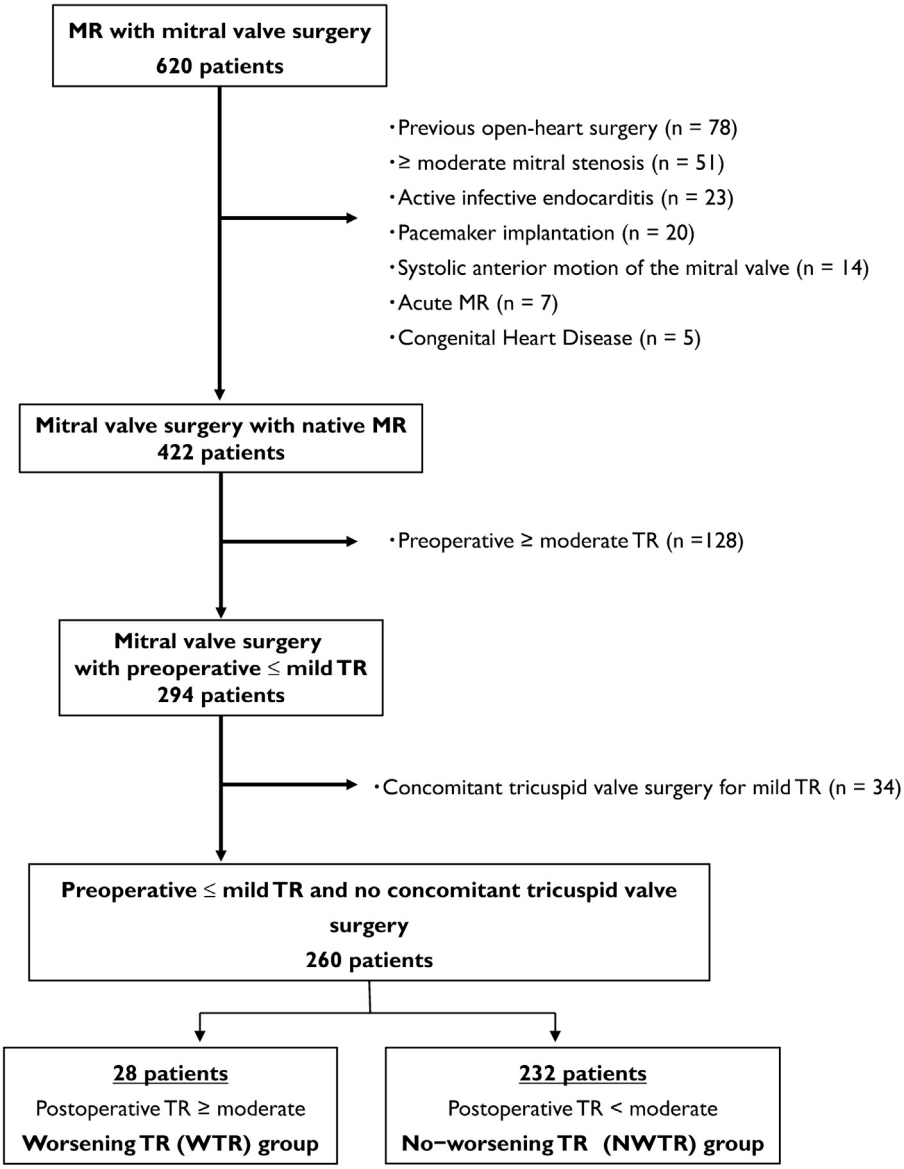

Figure 1. Flowchart of the study population. MR, mitral regurgitation; TR, tricuspid regurgitation.

severity was assessed qualitatively and quantitatively, and the regurgitant volume was measured using the proximal isovelocity surface area method or the Doppler volumetric method. TR severity was evaluated by color jet qualitative assessment on a 4-point scale, as follows: none (0), mild (1+), moderate (2+), and severe (3+), according to guidelines.[9,22] TAD was measured at late diastole in the apical 4-chamber view on transthoracic echocardiography. The TAD was also indexed to body surface area (TAD index) and the square root of body surface area. RA end-systolic area was measured according to the guidelines for the echocardiographic assessment of the right heart.[24]

Endpoints

The primary endpoint was postoperative worsening of ≥moderate TR. The secondary endpoint was cardiac events, defined as a composite of cardiac death, hospitalization due to heart failure, and postoperative worsening of ≥moderate TR. Death was regarded as being of cardiac origin unless obvious noncardiac causes were identified. Hospitalization for heart failure was defined as hospitalization due to worsening left-sided or right-sided heart failure requiring intravenous drug therapy. The TR grade was evaluated at discharge following surgery, and at 1, 3, 5, and 7 years postoperatively. Data collection was censored in February 2021.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and were compared between the 2 groups using the Wilcoxon rank-sum test. Categorical data are presented as number (percent) and were compared using Pearson's χ^2 test or Fisher's exact test. Two-sided

Table 1. Patients' Characteristics

	WTR Group (n = 28)	NWTR Group (n = 232)	*P* value
Clinical backgrounds			
Age, years	66 ± 9	59 ± 14	0.006
Sex (female), n (%)	15 (54)	53 (23)	<0.001
Body surface area, m^2	1.57 ± 0.22	1.68 ± 0.19	0.007
NYHA class Ⅲ/Ⅳ, n (%)	3 (11)	14 (6)	0.34
Hypertension, n (%)	17 (61)	120 (52)	0.37
Diabetes mellitus, n (%)	3 (11)	20 (9)	0.71
Dyslipidemia, n (%)	11 (39)	77 (33)	0.52
Smoking habits, n (%)	9 (32)	108 (47)	0.15
AMI, n (%)	1 (4)	10 (4)	0.85
Post-PCI, n (%)	2 (7)	16 (7)	0.96
Atrial fibrillation, n (%)	7 (25)	45 (19)	0.48
Paroxysmal atrial fibrillation, n (%)	3 (11)	25 (11)	0.99
MR etiology			
Degenerative, n (%)	25 (89)	200 (86)	0.83
Ventricular functional, n (%)	3 (11)	30 (13)	
Atrial functional, n (%)	0 (0)	2 (1)	
TR etiology			
Functional, n (%)	28 (100)	232 (100)	–
Laboratory data			
Hemoglobin, g/dL	13.2 (12.1–13.9)	13.8 (12.7–14.6)	0.015
Creatinine, mg/dL	0.85 (0.64–1.15)	0.89 (0.76–1.02)	0.52
Brain natriuretic peptide, pg/mL	87 (56–208)	56 (25–125)	0.005
Medication			
ACE-I/ARB, n (%)	3 (11)	69 (30)	0.034
Beta-blocker, n (%)	20 (71)	155 (67)	0.62
MRA, n (%)	21 (75)	183 (79)	0.64
Loop diuretic, n (%)	26 (93)	199 (86)	0.30

ACE-I, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin Ⅱ receptor blocker; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NWTR, nonworsening TR; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TR, tricuspid regurgitation; WTR, worsening TR.

P values of <0.05 were considered statistically significant. The Cox regression analysis was used to estimate the hazard ratios (HRs) in the worsening TR (WTR) group and in the nonworsening TR (NWTR) group. The variables to be analyzed were selected based on the factors with significant differences in baseline echocardiographic data and the previous reported factors for surgical indication (AF and TAD/TAD index). As the indicator of LA size, LA volume index (LAVI) was selected because of the 3-dimensional evaluation. The best multivariable model was selected by backward selection with the Akaike information criterion using variables in the univariable analysis after excluding the factors with VIF (variance inflation factor) >10 due to collinearity. The receiver operating characteristic curve analysis was performed to investigate the sensitivity and specificity of TR worsening during follow-up after surgery and to determine the best cut-off value for LAVI. The Kaplan–Meier method was used to estimate cumulative event-free survival, and the survival curves were compared between the 2 groups using the log-rank test. All statistical analyses were performed using JMP software, version 15 (SAS Institute Inc., Cary, NC, USA) and R 4.1.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients' Baseline Characteristics and Outcomes

The median follow-up period was 4.1 years (IQR: 2.9–6.1 years). Postoperative worsening of ≥moderate TR was detected in 28 patients (the WTR group). The other 232 patients did not show postoperative worsening of TR (the NWTR group).

The clinical features of the 2 groups are summarized in Table 1. Patients in the WTR group were older (66 ± 9 years vs 59 ± 14 years, $P = 0.006$) and had a smaller body surface area (1.57 ± 0.22 m^2 vs 1.68 ± 0.19 m^2, $P = 0.007$) than patients in the NWTR group. Moreover, the prevalence of the female sex and the value of brain natriuretic peptide were higher in the WTR group than in the NWTR group (female: 54% vs 23%, $P < 0.001$; brain natriuretic peptide: 87 [56–208] pg/mL vs 56 [25–125] pg/mL, $P = 0.005$). No significant difference in MR etiology was found between the 2 groups. Preoperative TR etiology was functional in all patients, and no patients with postoperative worsening of moderate TR got worse to severe TR during the intermediate follow-up periods.

Table 2. Echocardiographic and Right Heart Catheterization Data

	WTR Group	NWTR Group	*P* value
Echocardiographic parameters	n = 28	n = 232	
LV end-diastolic dimension, mm	59 ± 7	59 ± 7	0.82
LV end-systolic dimension, mm	39 ± 9	39 ± 8	0.76
LV ejection fraction, %	60 ± 11	58 ± 12	0.31
LA diameter, mm	51 ± 9	46 ± 7	0.013
LA volume index, mL/m^2	85 (62−117)	67 (54−81)	0.003
TRPG, mm Hg	33 ± 9 (n = 27)	28 ± 11 (n = 171)	0.003
E-wave velocity, m/s	1.22 ± 0.28	1.15 ± 0.33	0.26
e' (average), cm/s	8.7 ± 3.7	9.5 ± 3.6	0.12
E/e' (average), unit	15.9 ± 6.7	13.5 ± 5.6	0.059
MR regurgitant volume, mL	63 ± 14	62 ± 16	0.38
MR effective regurgitant orifice area, mm^2	42 ± 13	41 ± 14	0.83
TAPSE, mm	21.7 ± 5.2	21.7 ± 5.5	0.98
RV FAC, %	37 ± 7	36 ± 7	0.49
RV end-diastolic dimension (PLAX RVOT), mm	29 ± 5	31 ± 5	0.090
RV end-diastolic dimension (RV inflow mid), mm	33 ± 5	34 ± 6	0.12
Tricuspid annular diameter, mm	33 ± 5	34 ± 5	0.49
Tricuspid annular diameter index, mm/m^2	21.3 ± 3.7	20.2 ± 3.6	0.12
Tricuspid annular diameter/$\sqrt{}$BSA, mm/m	26.4 ± 3.7	26.0 ± 4.1	0.63
RA end-systolic area, cm^2	13.8 ± 3.3	14.6 ± 3.5	0.28
Right heart catheterization data	n = 23	n = 193	
Mean PCWP, mm Hg	12 (10−16)	11 (8−16)	0.36
PCWP V wave, mm Hg	18 (15−32)	19 (13−30)	0.90
Systolic PAP, mm Hg	31 (27−44)	29 (24−38)	0.062
Mean PAP, mm Hg	21 (17−24)	18 (14−25)	0.15
Mean RAP, mm Hg	4 (3−6)	4 (2−6)	0.38
Cardiac output (Fick), L/min	4.5 (4.1−5.0)	5.1 (4.0−6.0)	0.14

BSA, body surface area; FAC, fractional area change; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; NWTR, nonworsening TR; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PLAX, parasternal long-axis; RA, right atrial; RAP, right atrial pressure; RV, right ventricle; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient; WTR, worsening TR.

In the overall cohort, the secondary endpoint of cardiac events occurred in 48 patients, including cardiac death occurred in 2 patients, hospitalization due to heart failure occurred in 20 patients with left heart failure, and postoperative worsening of ≥moderate TR occurred in 26 patients.

Preoperative Echocardiography, Right Heart Catheterization, and Surgical Procedure

The preoperative echocardiographic parameters and right heart catheterization data are shown in Table 2. The LA diameter (LAD), LAVI, and tricuspid regurgitation pressure gradient (TRPG) were higher in the WTR group than in the NWTR group (LAD: 51 ± 9 mm vs 46 ± 7 mm, $P = 0.013$; LAVI: 85 [62−117] mL/m^2 vs 67 [54−81] mL/m^2, $P = 0.003$; TRPG: 33 ± 9 mm Hg vs 28 ± 11 mm Hg, $P = 0.003$). No significant differences in ventricular size and function and in MR severity were observed between the 2 groups. In terms of the preoperative right heart catheterization data, the mean pulmonary artery pressure tended to be higher in the WTR group than in the NWTR group, although no significant differences were noted in the other parameters, including the V wave of pulmonary capillary wedge pressure, mean right atrial pressure, and cardiac output.

The surgical procedures are shown in Table 3. Mitral valve plasty and minimally invasive cardiac surgery were performed in 24 patients (86%) and 9 patients (32%), respectively, in the WTR group, and in 218 patients (94%) and 102 patients (44%), respectively, in the NWTR group ($P = 0.10$ and $P = 0.23$, respectively). There were no significant differences in concomitant procedures, including the maze procedure, between the WTR group and the NWTR group (25% vs 16%, respectively, $P = 0.23$).

Predictors of Postoperative Worsening of TR

In the univariate Cox regression analysis, age, female sex, body surface area, LAVI, TRPG, TAD index were predictors of postoperative worsening of TR, whereas AF and TAD were not significant predictors (Table 4). In the multivariable Cox regression analysis adjusted for age and sex, LAVI and TRPG were significant predictors of postoperative worsening of TR (LAVI: HR 1.17 per 10-mL/m^2 increment, 95% confidence interval [CI] 1.07−1.26, $P < 0.001$; TRPG: HR 1.04 per 1-mm Hg increment, 95% CI 1.00−1.07, $P = 0.017$). Conversely, AF,

Table 3. Surgical procedures

	WTR Group (n = 28)	NWTR Group (n = 232)	*P* value
Surgical procedure for the mitral valve			
Mitral valve plasty, n (%)	24 (86)	218 (94)	0.10
Mitral valve replacement, n (%)	4 (14)	14 (6)	0.10
MICS, n (%)	9 (32)	102 (44)	0.23
Concomitant procedure			
CABG, n (%)	7 (25)	47 (20)	0.56
Maze procedure, n (%)	7 (25)	37 (16)	0.23
Aortic valve surgery, n (%)	2 (7)	17 (7)	0.97

CABG, coronary artery bypass grafting; MICS, minimally invasive cardiac surgery; NWTR, nonworsening TR; WTR, worsening TR.

Table 4. Cox Regression Analysis for Postoperative TR Worsening

Variables	Univariable Analysis		Age- and Sex-Adjusted Analysis		Multivariable Analysis*			
					Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (1-year increment)	1.05 (1.02−1.09)	0.004			1.05 (1.02−1.10)	0.003	1.04 (1.01-1.08)	0.02
Female sex	4.57 (2.13−9.80)	<0.001			3.53 (1.61−7.72)	0.002	3.26 (1.47-7.21)	0.004
Body surface area (1 m^2 increment)	0.08 (0.02−0.41)	0.002	1.77 (0.09−39.56)	0.72				
Atrial fibrillation	1.33 (0.56−3.16)	0.51	1.02 (0.42−2.45)	0.97				
LAVI (10 mL/m^2 increment)	1.17 (1.07−1.26)	<0.001	1.21 (1.10−1.32)	<0.001	1.21 (1.10−1.32)	<0.001		
LA enlargement (LAVI >79 mL/m^2) †	3.81 (1.78−8.17)	<0.001	3.42 (1.59−7.37)	0.002			3.42 (1.59−7.37)	0.002
TRPG (1 mm Hg increment)	1.05 (1.01−1.07)	0.002	1.04 (1.00−1.07)	0.017				
TAD (1 mm increment)	1.01 (0.94−1.08)	0.86	1.03 (0.95−1.12)	0.50				
TAD index (1 mm/m^2 increment)	1.14 (1.03−1.26)	0.012	1.03 (0.91−1.16)	0.63				

LAVI, left atrial volume index; TAD, tricuspid annular diameter; TRPG, tricuspid regurgitation pressure gradient.
*The best model was selected by backward selection with the Akaike information criterion using variables in the univariable analysis after excluding body surface area, TAD, and TAD index due to collinearity (VIF (variance inflation factor) >10). Regarding LAVI, continuous variables were analyzed in Model 1 and categorial variables of LAVI >79 mL/m^2 or not were analyzed in Model 2 respectively.
†The cut-off value was analyzed using the receiver operating characteristic curve analysis.

TAD, and TAD index were not associated with postoperative worsening of TR. The receiver operating characteristic analysis was performed for predicting postoperative worsening of TR after surgical operation. The area under the curve based on a LAVI was 0.69, and LAVI >79 mL/m^2 predicted prognosis with a sensitivity of 64.3% and specificity of 72.4%.

In the multivariate analysis using continuous variables of LAVI, age, female sex, and LAVI were significant predictors of postoperative worsening of TR (age: HR 1.05 per 1-year increment, 95% CI 1.02−1.10, $P = 0.003$; female sex: HR 3.53, 95% CI 1.61−7.72, $P = 0.002$; LAVI: HR 1.21 per 10 mL/m^2 increment, 95% CI 1.10−1.32, $P < 0.001$) (Table 4; model 1). In the multivariable analysis using categorial variables of LAVI >79 mL/m^2 or not, age, female sex, and LAVI (>79 mL/m^2) were also significant predictors of postoperative worsening of TR (age: HR 1.04 per 1-year increment, 95% CI 1.01−1.08, $P = 0.02$; female sex: HR 3.26, 95% CI 1.47−7.21, $P = 0.004$; LA enlargement [LAVI >79 mL/m^2]: HR 3.42, 95% CI 1.59−7.37, $P = 0.002$) (Table 4; model 2).

Clinical Outcomes of LAVI and AF

The Kaplan−Meier analysis showed that a high LAVI (>79 mL/m^2) was associated with significantly lower rates of freedom from postoperative worsening of TR and cardiac events compared with a low LAVI of ≤79 mL/m^2 (postoperative worsening of TR: 82.6% vs 93.9% at 5 years, log-rank $P = 0.008$; cardiac events: 68.5% vs 88.0% at 5 years, log-rank $P = 0.005$) (Figure 2A and Supplementary Figure 1A, and Figure 2B and Supplementary Figure 1B, respectively). Conversely, AF was not associated with postoperative worsening of TR or with the occurrence of cardiac events (Figure 3A and Supplementary Figure 2A, and Figure 3B and Supplementary Figure 2A, respectively).

DISCUSSION

The main findings of the present study are as follows: (1) postoperative worsening of TR occurred in 11% of patients with ≤mild preoperative TR without concomitant tricuspid annuloplasty during an intermediate follow-up period of 4.1

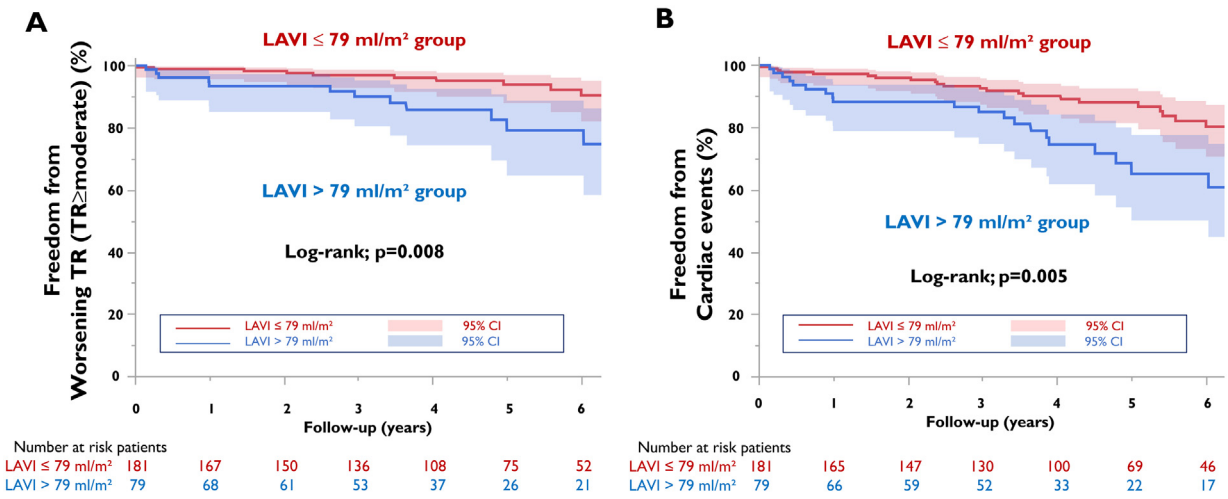

Figure 2. Clinical outcomes of LAVI. Kaplan–Meier curves of the rates of freedom from the primary and secondary endpoints (A, B) in the 2 groups of patients with LAVI cut-off values of >79 mL/m^2 or ≤79 mL/m^2. LAVI, left atrial volume index; CI, confidence interval. (Color version of figure is available online.)

years; (2) age, female sex, and LA enlargement were predictors of postoperative worsening of TR; and (3) a high LAVI (>79 mL/m^2) was associated with a significantly lower rate of freedom from postoperative worsening of TR and cardiac events than a low LAVI (≤79 mL/m^2) (Figure 4).

Incidence of TR Worsening After Mitral Valve Surgery in Patients with ≤Mild Preoperative TR

The incidence of significant TR after left-sided valve surgery is 7–27% according to previous studies.[4,25] However, the incidence is as high as 14–43% in limited patients after mitral valve surgery, which have demonstrated worsening of significant TR in patients after mitral valve surgery during long-term follow-up.[4,26] In the present study, the incidence of postoperative TR worsening was comparatively low (11% during the median follow-up period of 4.1 years) compared with previous reports, likely because preoperative TR severity was limited to ≤mild and the follow-up period was comparatively short. In a recent randomized controlled trial investigating the necessity of concomitant tricuspid annuloplasty in patients with severe MR and ≤moderate TR, the incidence of TR worsening without tricuspid annuloplasty was 6.1% over a 2-year follow-up period.[10] Therefore, the results of the present study in the early term after surgery are permissible.

Relationship Between Clinical Background and TR Worsening

Previous studies have reported that age and the female sex are associated with the occurrence of significant TR in patients with a natural history of TR,[1,2,27] as well as in patients after

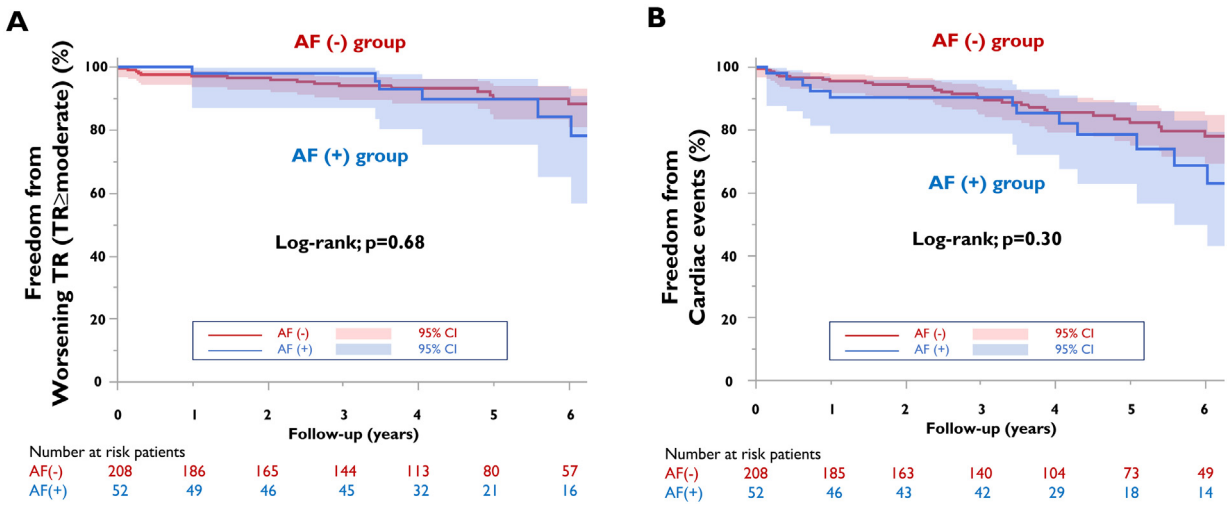

Figure 3. Clinical outcomes of AF. Kaplan–Meier curves of the rates of freedom from the primary and secondary endpoints (A, B) in the two groups of patients with or without AF. AF, atrial fibrillation; CI, confidence interval. (Color version of figure is available online.)

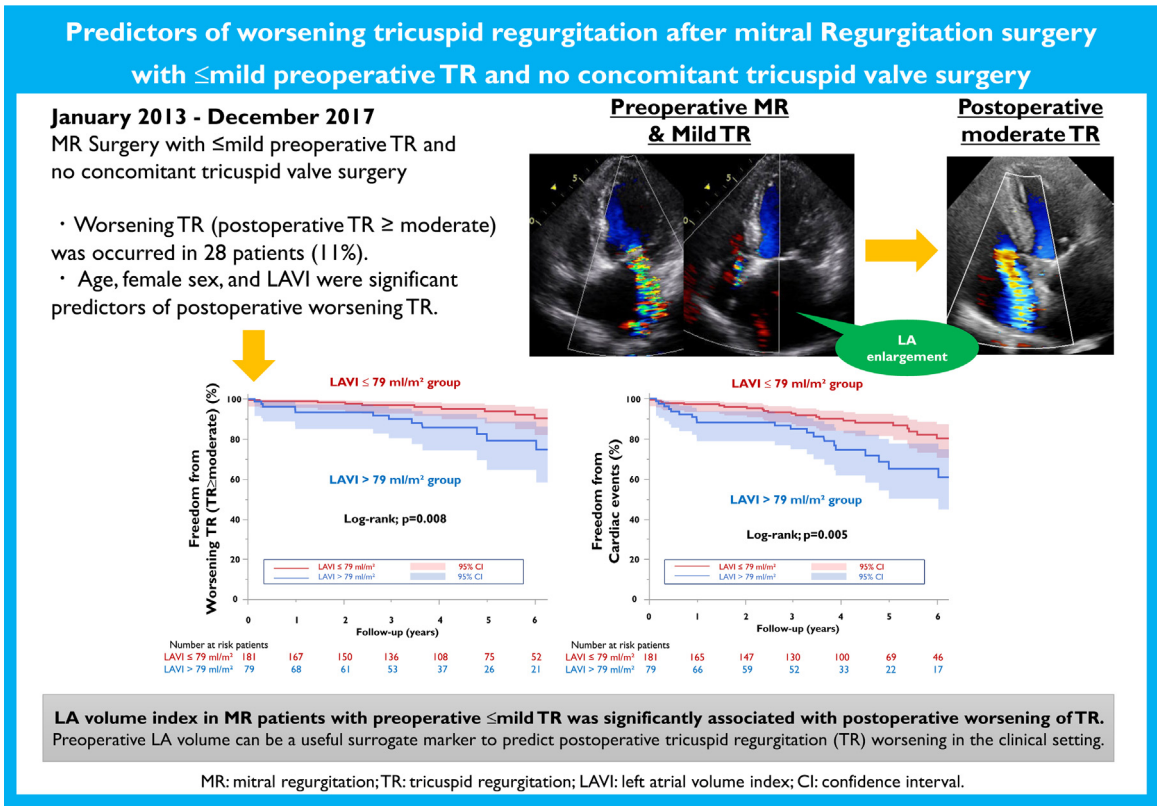

Figure 4. The indications for concomitant surgery for ≤mild tricuspid regurgitation (TR) in patients undergoing mitral valve surgery have not been fully elucidated. The present study evaluated the prevalence and predictors of postoperative TR worsening in patients with concomitant ≤mild TR undergoing mitral regurgitation surgery. Postoperative worsening of TR occurred in 11% of patients during intermediate-term follow-up. Age, female sex, and LA volume index (LAVI) were significant predictors of the primary outcome. A high LAVI (>79 mL/m^2) was significantly associated with a low rate of freedom from postoperative TR worsening. Preoperative LA volume can be a useful surrogate marker to predict postoperative tricuspid regurgitation (TR) worsening in the clinical setting. MR, mitral regurgitation; TR, tricuspid regurgitation; LAVI, left atrial volume index; CI, confidence interval. (Color version of figure is available online.)

mitral valve surgery.[12,28] In particular, age is an important factor because left ventricular diastolic dysfunction and AF with aging induce pulmonary hypertension and TA dilatation,[29,30] resulting in an increase in the rate of TR worsening. In the present study, age and the female sex were also associated with postoperative TR worsening. Therefore, regardless of tricuspid valve surgery, older females may be at a particularly high risk of TR worsening.

Relationship Between LAVI and TR Worsening

In patients with significant MR, LA enlargement, especially a LAVI of ≥60 mL/m^2, is associated with a poor prognosis.[31,32] The main mechanism of LA dilatation in patients with significant MR is long-standing regurgitant flow from the left ventricle into the left atrium. Thus, LA dilatation directly reflects the severity and duration of MR. A previous report showed that patients with significant MR and LA enlargement often present with pulmonary hypertension due to LA dysfunction.[33] Therefore, patients with LA enlargement after MR surgery are more likely to develop pulmonary hypertension and right ventricular dysfunction and dilatation, resulting in postoperative TR worsening due to tricuspid valve tethering and/or TA dilatation. No reports have investigated the association between LA volume and postoperative TR worsening, although LAD (>60 mm) is related to TR worsening after mitral valve surgery.[11] In general, LA volume is a better marker than LAD; thus, the results of the present study may contribute to establishing a new surgical indication for concomitant tricuspid valve surgery in patients with significant MR and mild TR.

AF was not associated with postoperative TR worsening, although it is a well-known cause of LA dilatation. Previous studies have shown that AF is associated with TR worsening after mitral valve surgery,[4,11,12,34] but the follow-up periods of these studies were longer than the follow-up period in the present study. Moreover, maze procedures are recommended for concomitant AF,[14] and the procedures are associated with good postoperative outcomes.[35] Therefore, an intermediate-term follow-up period and the widely used maze procedures might explain why AF was not a prognostic factor for TR worsening in the present study.

Validity of TAD and TAD Index Cut-off Values as Indications for Concomitant Surgery

The validity of a TAD of >40 mm or a TAD index of >21 mm/m^2 as the cut-off value for concomitant tricuspid valve surgery has been controversial. Previous studies[17,19] have shown negative data on the relationship between TAD and postoperative TR worsening, and the results of the present study show that postoperative TR worsening cannot be determined using TAD alone. The recent relevant study have showed that preoperative TAD of 40−44 mm was not associated with late recurrent TR excluding patients with ultimately large TAD of ≥45 mm.[34] Conversely, a previous report revealed that the TAD index (but not TAD) was an independent predictor of postoperative TR worsening (≥moderate) in patients with preoperative mild-to-moderate TR without concomitant tricuspid annuloplasty.[5,18] In the present study, the TAD index (but not TAD) was also associated with postoperative TR worsening in the univariable analysis, although it was not an associated factor after adjustment for age and the female sex. The TAD index may be strongly affected by body surface area. The TAD index, in which the distance (TAD) is divided by the area (body surface area), may be overcorrected by body surface area, especially in the Asian population and in older females with a small body surface area. The TAD index cut-off value of 21 mm/m^2 is based on data from Europe[15]; thus, it is doubtful that the overcorrected value by body surface area can be used in the Asian population because Asian people tend to be smaller than their European and American counterparts. Therefore, a TAD cut-off value of >40 mm or a TAD index cut-off value of >21 mm/m^2 for concomitant tricuspid valve surgery in patients with ≤mild preoperative TR should be used cautiously in clinical situations.

Study Limitations

The present study had several limitations. First, this study was a retrospective single-center study, which may have led to selection bias. Moreover, the sample size was small. Thus, a randomized, multicenter, prospective study is needed to investigate whether LA volume can determine the usefulness of tricuspid valve surgery in patients with MR and concomitant ≤mild TR. Second, the interval of follow-up echocardiography was not determined, so the results may not reflect the exact onset of TR worsening, and the incidence of TR worsening may have been underestimated. Third, because the follow-up period was relatively short, other parameters may be related to TR worsening in studies with longer follow-up periods. Fourth, the TR grade was not quantified in this study, and qualitative assessment of TR severity based on TR color jet was used. However, this qualitative assessment is widely used in the clinic. Finally, TRPG could not be measured in all patients due to the targeting of patients with ≤mild TR.

CONCLUSIONS

In this study, the incidence of postoperative TR worsening was 11% in patients with ≤mild preoperative TR without concomitant tricuspid annuloplasty. LA enlargement was significantly associated with postoperative worsening of TR.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Tasuku Hada and Masashi Amano contributed to data collection. Tasuku Hada, Masashi Amano, Shunsuke Murata and Kunihiro Nishimura performed data analysis. Tasuku Hada, Masashi Amano and Chisato Izumi drafted the manuscript, which was critically revised by all authors. All authors read and approved the final manuscript for submission.

SUPPLEMENTARY MATERIAL

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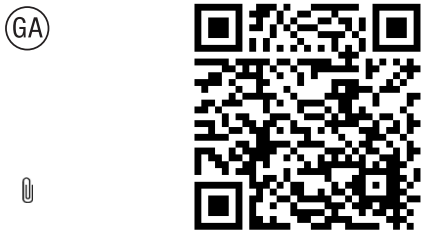

REFERENCES

1. Topilsky Y, Maltais S, Medina Inojosa J, et al: Burden of tricuspid regurgitation in patients diagnosed in the community setting. J Am Coll Cardiol Img 12:433–442, 2019
2. Prihadi EA, van der Bijl P, Gursoy E, et al: Development of significant tricuspid regurgitation over time and prognostic implications: New insights into natural history. Eur Heart J 39:3574–3581, 2018
3. Essayagh B, Antoine C, Benfari G, Maalouf J, Michelena HI, Crestanello JA, et al: Functional tricuspid regurgitation of degenerative mitral valve disease: A crucial determinant of survival. Eur Heart J 41:1918–1929, 2020
4. Izumi C, Miyake M, Takahashi S, et al: Progression of isolated tricuspid regurgitation late after left-sided valve surgery. Clinical features and mechanisms. Circ J 75:2902–2907, 2011
5. Goldstone AB, Howard JL, Cohen JE, et al: Natural history of coexistent tricuspid regurgitation in patients with degenerative mitral valve disease: Implications for future guidelines. J Thorac Cardiovasc Surg 148:2802–2809, 2014
6. Yajima S, Yoshioka D, Toda K, et al: Definitive determinant of late significant tricuspid regurgitation after aortic valve replacement. Circ J 82:886–894, 2018
7. Vahanian A, Beyersdorf F, Praz F, et al: 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 43:561–632, 2022
8. Otto CM, Nishimura RA, Bonow RO, et al: 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 143:e72–e227, 2021
9. Izumi C, Eishi K, Ashihara K, et al: JCS/JSCS/JATS/JSVS 2020 Guidelines on the management of valvular heart disease. Circ J 84:2037–2119, 2020
10. Gammie JS, Chu MWA, Falk V, et al: Concomitant tricuspid repair in patients with degenerative mitral regurgitation. N Engl J Med 386:327–339, 2022

11. Matsuyama K, Matsumoto M, Sugita T, et al: Predictors of residual tricuspid regurgitation after mitral valve surgery. Ann Thorac Surg 75:1826–1828, 2003
12. Song H, Kim MJ, Chung CH, et al: Factors associated with development of late significant tricuspid regurgitation after successful left-sided valve surgery. Heart 95:931–936, 2009
13. Dreyfus GD, Corbi PJ, Chan KM, et al: Secondary tricuspid regurgitation or dilatation: Which should be the criteria for surgical repair? Ann Thorac Surg 79:127–132, 2005
14. Hindricks G, Potpara T, Dagres N, et al: 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 42:373–498, 2021
15. Colombo T, Russo C, Ciliberto GR, et al: Tricuspid regurgitation secondary to mitral valve disease: Tricuspid annulus function as guide to tricuspid valve repair. Cardiovasc Surg 9:369–377, 2001
16. Benedetto U, Melina G, Angeloni E, et al: Prophylactic tricuspid annuloplasty in patients with dilated tricuspid annulus undergoing mitral valve surgery. J Thorac Cardiovasc Surg 143:632–638, 2012
17. David TE, David CM, Manlhiot C: Tricuspid annulus diameter does not predict the development of tricuspid regurgitation after mitral valve repair for mitral regurgitation due to degenerative diseases. J Thorac Cardiovasc Surg 155:2429–2436, 2018
18. Shi KH, Xuan HY, Zhang F, et al: Evolution of tricuspid regurgitation after mitral valve surgery for patients with moderate-or-less functional tricuspid regurgitation. Heart Surg Forum 15:E121–E126, 2012
19. Calafiore AM, Iacò AL, Romeo A, et al: Echocardiographic-based treatment of functional tricuspid regurgitation. J Thorac Cardiovasc Surg 142:308–313, 2011
20. Fujita T, Kobayashi J, Toda K, et al: Long-term outcome of combined valve repair and maze procedure for nonrheumatic mitral regurgitation. J Thorac Cardiovasc Surg 140:1332–1337, 2010
21. Lang RM, Bierig M, Devereux RB, et al: Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18:1440–1463, 2005
22. Nagueh SF, Appleton CP, Gillebert TC, et al: Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22:107–133, 2009
23. Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and doppler echocardiography. J Am Soc Echocardiogr 16:777–802, 2003
24. Rudski LG, Lai WW, Afilalo J, et al: Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 23:685–713, 2010.. quiz 786-788
25. Kwak JJ, Kim YJ, Kim MK, et al: Development of tricuspid regurgitation late after left-sided valve surgery: A single-center experience with long-term echocardiographic examinations. Am Heart J 155:732–737, 2008
26. Izumi C, Iga K, Konishi T: Progression of isolated tricuspid regurgitation late after mitral valve surgery for rheumatic mitral valve disease. J Heart Valve Dis 11:353–356, 2002
27. Singh JP, Evans JC, Levy D, et al: Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol 83:897–902, 1999
28. Porter A, Shapira Y, Wurzel M, et al: Tricuspid regurgitation late after mitral valve replacement: Clinical and echocardiographic evaluation. J Heart Valve Dis 8:57–62, 1999
29. Owan TE, Redfield MM: Epidemiology of diastolic heart failure. Prog Cardiovasc Dis 47:320–332, 2005
30. Inoue H, Fujiki A, Origasa H, et al: Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. Int J Cardiol 137:102–107, 2009
31. Rusinaru D, Tribouilloy C, Grigioni F, et al: Left atrial size is a potent predictor of mortality in mitral regurgitation due to flail leaflets: Results from a large international multicenter study. Circ Cardiovasc Imaging 4:473–481, 2011
32. Arias A, Pizarro R, Oberti P, et al: Prognostic value of left atrial volume in asymptomatic organic mitral regurgitation. J Am Soc Echocardiogr 26:699–705, 2013
33. von Roeder M, Rommel KP, Kowallick JT, et al: Influence of left atrial function on exercise capacity and left ventricular function in patients with heart failure and preserved ejection fraction. Circ Cardiovasc Imaging 10: e005467, 2017
34. McCarthy PM, Szlapka M, Kruse J, et al: The relationship of atrial fibrillation and tricuspid annular dilation to late tricuspid regurgitation in patients with degenerative mitral repair. J Thorac Cardiovasc Surg 161:2030–2040, 2021
35. Budera P, Straka Z, Osmancik P, et al: Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study. Eur Heart J 33:2644–2652, 2012