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ORIGINAL ARTICLE
Valvular heart disease

Causal relation of tricuspid regurgitation for heart failure outcomes: a mediation analysis of echocardiographic predictors

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Aims Although significant tricuspid regurgitation (TR) is critically associated with heart failure (HF) prognosis, the predictors for large TR impact on HF outcomes remain unknown. This study aimed to identify echocardiographic predictors for a causal relation of TR to HF outcomes.

Methods and results In a retrospective, acute HF cohort of 462 patients, multivariate logistic regression analysis was performed to determine subgroups with strong association of greater-than-moderate TR with HF readmission or cardiovascular death in a year. We then conducted causal mediation analysis according to persistent atrial fibrillation (Af) or mitral regurgitation (MR) to identify the echocardiographic predictors. The association of TR with HF outcomes was prominent in subgroups of females, with Af, the enlarged indexed tricuspid annular diameter (TADi) or right atrial area, or within certain ranges of the left ventricular ejection fraction, indexed right ventricular end-systolic area, or fractional area change (FAC). Causal mediation analysis found that the TR impact was significant in patients with Af. Furthermore, combination of TADi $\geq$2.1 cm/m^2 and FAC $\geq$30%, which accounted for half of TR patients, predicted a much larger TR impact irrespective of Af and MR. Its prediction ability was superior to that of the modified Model for End-stage Liver Disease score.

Conclusion The causal impact and burden of TR on HF outcomes was significant in patients with Af, and combining TADi $\geq$2.1 cm/m^2 with FAC $\geq$30% could provide superior echocardiographic prediction of larger TR impact in HF patients.

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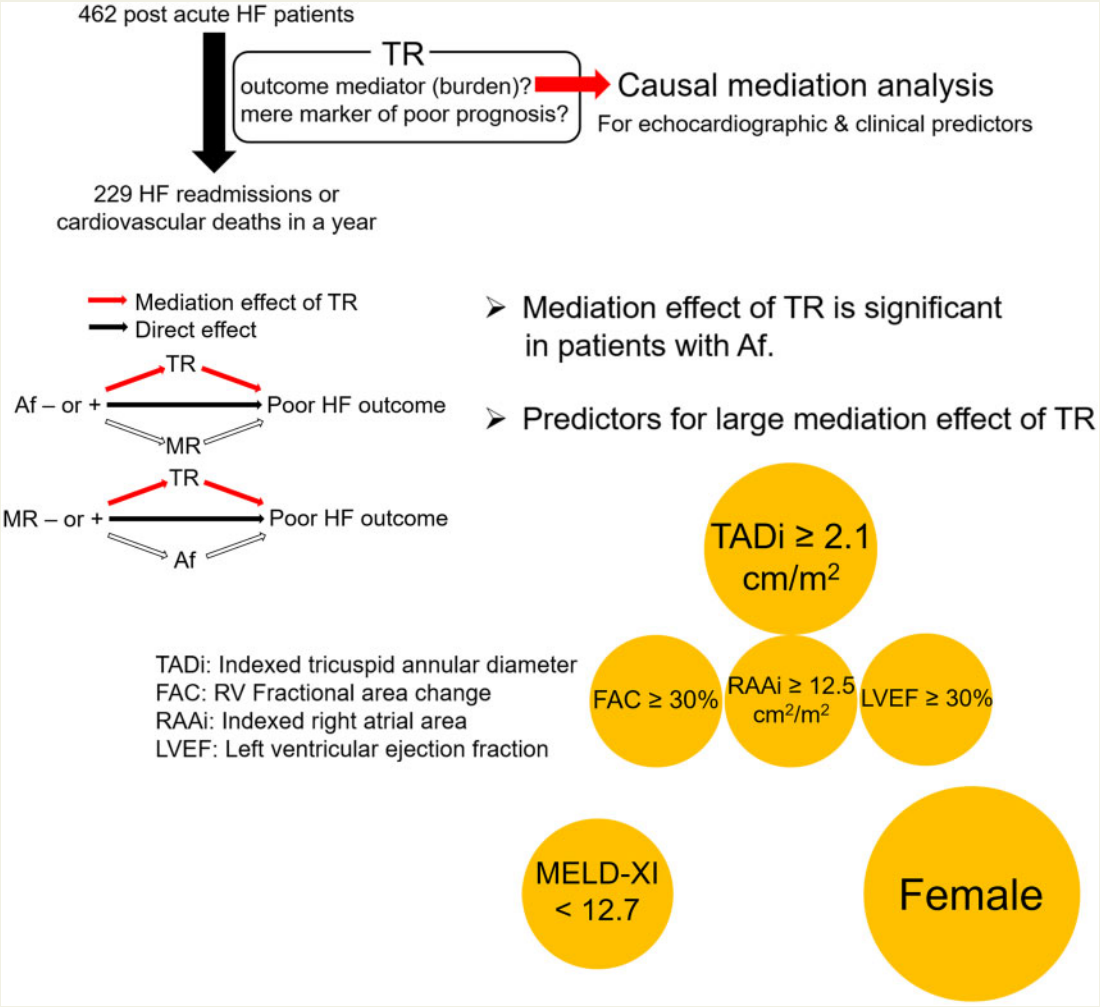
Graphical Abstract



Keywords Tricuspid regurgitation • Heart failure • Echocardiography • Predictor • Mediation analysis

Introduction

The tricuspid valve had long been considered a 'forgotten valve', and the pathophysiological role of tricuspid regurgitation (TR) had been poorly recognized in heart failure (HF). The frequency of greater-than-moderate TR increases with age, reaching 5% in patients >70 years old.[1] The aetiology of approximately 90% of TR is functional without primary valve lesions,[2] and two mechanisms are considered to cause functional TR: leaflet tethering by right ventricular (RV) dilatation/dysfunction or tricuspid annular (TA) dilatation.[3,4] A growing body of evidence has suggested that significant functional TR is associated with mortality and HF hospitalization in patients with mitral regurgitation (MR),[5] atrial fibrillation (Af),[6,7] after left-sided valve surgery,[8,9] or HF.[10]

Therapies for TR include diuretics and surgery such as annuloplasty and repair/replacement; however, transcatheter intervention has recently emerged as a possible option.[11] Nevertheless, TR is generally undertreated, and surgery for isolated TR is rarely performed, resulting in high mortality rates with an in-hospital mortality rate of approximately 9%.[12] One reason for this obstacle is that predictors for the magnitude of the causal impact of TR on the outcomes are unknown, making it difficult to select the optimal patients and timing (especially before the 'point of no return') of TR intervention.[13]

Previous studies have shown the mean pulmonary arterial pressure,[14] TA diameter (TAD),[15,16] RV end-systolic area (RVESA)[17] or end-diastolic mid-cavity diameter,[18] and modified Model for End-stage Liver Disease (MELD) score[19] as prognostic markers after TR surgery. Nevertheless, clinical and

echocardiographic indices predicting a causal impact of TR on HF outcomes remain unknown.

Causal mediation analysis can uncover possible mechanisms via the effect of mediators such as medical conditions or interventions.[20] Recent studies have applied causal mediation analysis to screen the mediators for the association of depression with poor sleep quality[21] and to study contrast-induced acute kidney injury as a mediator for the association of the pre-angiography estimated glomerular filtration rate (GFR) with adverse outcomes.[22]

In line with the above, this study highlighted mostly functional TR in an HF cohort and performed causal mediation analysis to identify the echocardiographic predictors for a large impact and burden of TR on HF outcomes.

Methods

Study design and population

This study examined a retrospective cohort of patients who were admitted for acute decompensated HF in Kawasaki Municipal Hospital from 1 April 2015 to 31 March 2018 as described previously.[23] We enrolled 662 consecutive patients with acute HF defined according to the modified Framingham criteria[24] but excluded those with acute coronary syndrome or who were on regular haemodialysis (*Figure 1*). The discharge date was set as the start time of follow-up, and we further excluded patients who could not undergo follow-up in our hospital as well as non-cardiovascular (CV) deaths in a year after discharge. We analysed the data of the remaining 462 patients as the HF cohort (*Figure 1*). Laboratory tests were conducted on admission and just prior to discharge, and other clinical data were obtained just prior to discharge. Transthoracic echocardiography was performed after HF was stabilized and compensated by the treatment including the diuretics (1 week to 1 month after admission) in the ultrasound department by registered medical sonographers or board-certified cardiologists of the Japanese Circulation Society. The ultrasound equipment used included the Vivid 7 (GE Healthcare Japan, Tokyo), and EPIQ 7C (Philips Japan, Tokyo). After HF stabilization, the patients received medication and/or surgery based on guidelines and their preferences.

This study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Clinical Trial/Clinical Research Ethics Review Board of Kawasaki Municipal Hospital (2018-27). The requirement for written informed consent was waived by the board, as the study met the Japanese ethical guidelines and the United States' policy for protecting human research participants.

Data collection

Data including outcomes, namely HF readmission or CV death within a year after discharge were retrospectively collected from electronic medical records by board-certified cardiologists. The final clinical follow-up was completed on 30 April 2019. The body surface area was calculated using the formula of Du Bois.[25] Coronary artery disease (CAD) was defined as prior myocardial infarction or prior history of percutaneous coronary intervention or coronary artery bypass graft surgery. The definitions of hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, and connective tissue disease and the calculation method for the estimated GFR were as previously described.[23] The MELD excluding the international normalized ratio (MELD-XI) score was calculated as $5.11 \times \ln$ (total bilirubin in mg/dL) $+ 11.76 \times \ln$ (creatinine in mg/dL) $+ 9.44$.[26]

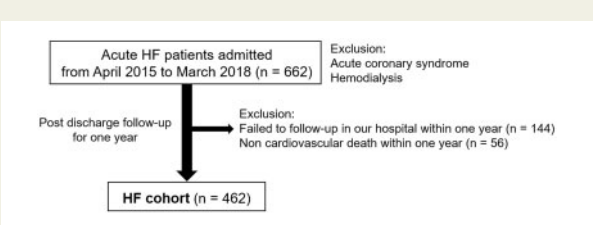


Figure 1 Study flowchart. Heart failure patients participated in this study. HF, heart failure.

Echocardiography

Echocardiographic parameters were quantified and reported based on the recommendation of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[27] The linear internal diameter of the left ventricle (LVD) was obtained in the parasternal long-axis view, and the left ventricular ejection fraction (LVEF) was calculated using the biplane disk summation method, or if it was impossible the Teichholz method as previously described.[23] The right atrial area (RAA) and TAD were measured in the apical four-chamber view at end-systole and end-diastole, respectively. The RV area and end-diastolic diameters of the basal and mid-cavity RV were acquired in the RV-focused apical four-chamber view to the extent possible according to the above recommendation. The fractional area change (FAC) of the RV, an index of RV global systolic function, was calculated as [RV end-diastolic area (RVEDA) - RVESA]/RVEDA $\times$ 100 (%). All measurements except the LVEF and FAC were adjusted to the body surface area, and the ranges of each parameter for univariate logistic regression analyses were decided based on the reference values in the USA and Europe[27] and Japan.[28] Several measurements were retrospectively performed in some patients by a board-certified fellow of the Japan Society of Ultrasonics in Medicine (D.H.) in a blinded manner. In the echocardiographic parameters, 18–30% of the data were missing because the body surface area or the appropriate views for measurement could not be obtained. Pulmonary hypertension (PH) was defined as peak flow velocity of TR $\geq$2.9 m/s according to the PH guideline in Europe.[29] The severity of TR and MR was graded by structural, qualitative (colour flow jet area and flow convergence zone), and semiquantitative [vena contracta width (VCW)] parameters according to the United States guideline.[30] Greater-than-moderate regurgitation with VCW $\geq$3 mm was considered as TR and/or MR. The VCW of TR was the average between parasternal RV inflow and apical four-chamber views with Nyquist limit 50–70 cm/s. There were no patients with TR caused by Ebstein's anomaly, infective endocarditis, rheumatic or myxomatous disease, or carcinoid in the cohort. All echocardiographic data were verified by a board-certified fellow of the Japan Society of Ultrasonics in Medicine (D.H.).

Outcome

The outcome was HF readmission or CV death in a year after discharge. Heart failure readmission was defined as worsening of HF requiring intravenous drugs and/or extra oxygen administration. Cardiovascular death included sudden death and death related to HF, strokes, or other CV causes.

Statistical analysis

Categorical variables were presented as percentages and compared using the Fisher's exact test. Continuous variables were expressed as means with standard deviations or medians with interquartile ranges depending on their distribution and were compared using unpaired *t*-tests or Mann–Whitney *U* tests. Patients with missing values were excluded from logistic

regression analyses or causal mediation analyses by listwise deletion to perform available case analysis. For these analyses, continuous variables were dichotomized or grouped by clinically meaningful values or mean/median values. Variance inflation factors <2 were confirmed for excluding multicollinearity in multivariate logistic regression analyses. We further performed logistic regression analyses with interaction tests among clinically relevant subgroups.

Causal mediation analysis consists of three regression analyses among the effector, mediator(s), and outcome and estimates the direct and indirect (mediation) effects and the proportion mediated in a specific mediator.[20] The amount of the estimate of the indirect effect is proportional to the magnitude of the causal mediation effect (CME) on the outcome. Furthermore, adding the alternative mediator to the analysis allows assessing the effect of the main mediator under the confounding alternative mediator. Causal mediation analysis was conducted using the mediation package ver. 4.5.0 in the R software ver. 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria). The 95% confidence intervals (CIs) were tested using the non-parametric bootstrap with 2000 simulations, and a lower CI >0 was considered significant. We decided the cut-off value of MELD-XI score based on its receiver operating characteristic curve regarding HF outcomes.

All statistical analyses, except causal mediation analysis, were performed using the EZR, ver. 1.42, which is a modified version of R.[31] A two-sided $P < 0.05$ was considered statistically significant.

Results

Specific subgroups with strong association of tricuspid regurgitation with worse outcomes in the heart failure cohort

We first screened to identify the subgroups in which there was a strong association between TR and HF outcomes in the HF cohort (*Figure 1*). In this cohort, the median age of patients was 78 years, 54.3% were male, and two-thirds had prior HF admission (*Table 1*). The average LVEF was 47.8%, and the proportion of patients with greater-than-moderate MR or TR was 17.9% or 20.4%, respectively. There were 29 CV deaths in a year. Patients with CV events were older, more frequently female, had prior HF admission, CAD, diabetes mellitus, PH, TR, and larger indexed diameters of the LV, TA, and RV than patients without CV events.

Univariate logistic regression analyses found that the odds ratio (OR) of TR on worse HF outcome was 2.37 (95% CI 1.4–4.01, $P = 0.001$) (Supplementary material online, *Figure S1a*). Subgroup analyses regarding clinical (Supplementary material online, *Figure S1a*) and echocardiographic (Supplementary material online, *Figure S1b*) indices showed that there was a significant subgroup interaction in age and a trend of interaction in CAD. Interestingly, the OR of TR was not significant in the subgroups of age ≥80 years old, CAD, LVEF <30%, indexed end-diastolic LVD ≥3.1 cm/m^2, indexed RAA (RAAi) <12.5 cm^2/m^2, indexed TAD (TADi) <2.1 cm/m^2, indexed RVESA (RVESAi) ≥9.5 cm^2/m^2, or FAC <30%.

Based on these findings, we set the ranges of several echocardiographic indices and performed multivariate logistic regression analyses on HF outcomes (*Figure 2*). The variables included were age, sex, prior HF admission, persistent Af, CAD, LVEF, PH, MR, and TR. The OR of TR was 2.72 (95% CI 1.22–6.09, $P = 0.015$), and subgroup analyses by clinical (*Figure 2A*) and echocardiographic (*Figure 2B*) indices revealed similar results as those of the univariate analyses. There was a significant subgroup interaction in age and TADi, and a trend of interaction in RAAi and RVESAi.

These results suggest that the association of TR with HF outcome is most prominent in the subgroups above the cut-off values of the RAAi or TADi, or within certain ranges of the LVEF, RVESAi, or FAC.

Identification of subgroups with a large causal mediation effect of tricuspid regurgitation on heart failure outcome

To analyse the causal relation of TR for HF outcomes and identify specific subgroups with a large TR impact, causal mediation analyses were performed. Considering the above results and clinical relevance, we set the main mediator of TR, and the alternative mediator of MR (a schema in *Figure 3A*) or persistent Af (a schema in *Figure 3B*) for HF outcomes. These settings allow us to assess the magnitude of the pure CME of TR and direct effect not through TR according to the presence or absence of persistent Af or MR.

As shown in *Figure 3A* and *B*, the CME which was larger than the direct effect was significant in patients with Af (0.94, 95% CI 0.16–1.7, $P < 0.05$). The CME also showed a trend of significance in patients with or without MR (0.57, 95% CI -0.1 to 1.2 or 0.3, 95% CI -0.07 to 0.7, respectively).

Next, we examined subgroup disparity in the magnitude of the CME regarding clinical and echocardiographic indices. In patients with Af, the CME was significant and/or prominent in the subgroups of female patients (1.83, 95% CI 0.25–3.4) and those with prior HF admission (1.05, 95% CI 0.12–2), LVEF ≥30% (1.07, 95% CI 0.19–1.9), TADi ≥2.1 cm/m^2 (1.35), RVESAi <9.5 cm^2/m^2 (1.05, 95% CI 0.17–1.9), or FAC ≥30% (1.09, 95% CI 0.19–2) (*Figure 3C*).

To validate if these predictors are causally related independently of TR severity, the severity was compared in each subgroup by the rate of TR with VCW ≥7 mm, which indicates severe TR, and the median VCW (*Table 2*). The median VCW was significantly higher in patients with Af than in those without Af, while the rate of severe TR (VCW ≥ 7 mm) and the median VCW showed no difference in patients with or without MR. In patients with Af, subgroups of females, prior HF admission, RAAi ≥12.5 cm^2/m^2, or TADi >2.1 cm/m^2 had more severe TR than their counterparts, whereas the subgroup of RVESAi <9.5 cm^2/m^2 had fewer severe TR. The difference in TR severity was not significant in the remaining subgroups. We found that the average CME of severe TR in subgroups of females, prior HF admission, RAAi ≥12.5 cm^2/m^2, or TADi >2.1 cm/m^2 (1.17, 0.43, 0.65, 0.81, respectively) remained larger than that in the entire patients with Af (0.38) (Supplementary material online, *Table S1*). Furthermore, TR severity is similar in patients with and without Af if VCW ≥5 mm is regarded as TR. In this case, the profile of the average CMEs in subgroups with Af was almost the same as that in the original cohort (Supplementary material online, *Table S2*). Therefore, the identified predictors appeared independent of TR severity.

These findings indicate that the CME of TR is significant in patients with Af, and that the echocardiographic indices including the LVEF, TADi, and FAC predict a large TR impact.

Table 1 Baseline demographics of patients in the HF cohort

Clinical variables	All ($n = 462$)	HF readmission or cardiovascular death in a year (−) ($n = 233$)	(+) ($n = 229$)	*P*-value
Age (years)	78 (69–84)	75 (66–82)	80 (75–86)	<0.001
Male	54.3	59.7	48.9	0.025
Body surface area (m^2)	1.53 (0.23)	1.58 (0.23)	1.49 (0.22)	<0.001
Prior HF admission	67.1	52.8	81.7	<0.001
Prior left-sided valve surgery	13.6	9.9	17.5	0.021
CAD	38.7	29.6	48	<0.001
Persistent Af	31.2	29.2	33.2	0.367
Pacemaker/ICD/CRTD	11.7	12	11.3	0.771
NYHA				
2	29.4	35.2	23.6	<0.001
3	60.2	49.8	70.7	
4	2.2	0	4.4	
Hypertension	61.3	64.8	57.6	0.127
Diabetes mellitus	45.7	34.8	56.8	<0.001
Chronic kidney disease	58	45.9	70.3	<0.001
COPD	11.7	10.7	12.7	0.564
Connective tissue disease	3.9	5.2	2.6	0.229
Loop diuretic	84.6	82.8	86.6	0.296
Furosemide equivalent (mg/day)	40 (20–80)	40 (20–60)	40 (20–80)	0.165
ACE inhibitor/ARB	53.5	60.9	45.4	0.001
β blocker	72.4	73.8	70.8	0.527
BNP (pg/mL)	836 (448–1520)	719 (408–1279)	1023 (538–1732)	0.002
Lymphocyte (cells/μL)	1489 (597)	1596 (633)	1360 (526)	<0.001
Haemoglobin (g/dL)	11.8 (2.3)	12.3 (2.3)	11.2 (2.1)	<0.001
Total bilirubin (mg/dL)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.5 (0.4–0.8)	0.238
estimated GFR (mL/min/1.73 m^2)	45.2 (25.5)	49.9 (25.2)	39.9 (24.8)	<0.001
MELD-XI score (points)	11.6 (9.4–15.7)	10.6 (9.4–14.6)	13.4 (9.4–17.6)	<0.001
Echocardiographic variables				
MR	17.9	15.9	20.7	0.266
PH	19	14.8	24.7	0.028
TR	20.4	14.5	28.7	0.001
Vena contracta width of TR (mm)	5.0 (4.0–7.9)	5.0 (4.0–7.1)	6.0 (4.0–8.0)	0.229
LVEF (%)	47.8 (17.1)	48.6 (17.1)	46.6 (16.9)	0.26
LVEF ≥50%	50.4	52.6	47.5	0.35
LVDdi (cm/m^2)	3.41 (0.67)	3.3 (0.59)	3.57 (0.76)	<0.001
RAAi (cm^2/m^2)	9.57 (7.83–12.81)	9.21 (7.73–12.43)	10.35 (8.26–13.28)	0.03
TADi (cm/m^2)	1.8 (0.36)	1.75 (0.36)	1.88 (0.36)	0.003
RVDi base (cm/m^2)	2.27 (0.49)	2.2 (0.47)	2.38 (0.51)	0.002
RVDi mid (cm/m^2)	1.52 (0.4)	1.48 (0.37)	1.59 (0.43)	0.014
RVEDAi (cm^2/m^2)	9.05 (7.63–10.93)	9 (7.63–10.58)	9.44 (7.63–11.6)	0.102
RVESAi (cm^2/m^2)	4.77 (3.86–6.05)	4.65 (3.90–5.96)	5.07 (3.76–6.52)	0.182
FAC (%)	45.7 (10)	45.3 (10.4)	46.1 (9.6)	0.49

Values are percentage, mean (SD), or median (interquartile range) unless otherwise noted. BNP is examined on HF admission, and the others are at discharge. The grade of MR or TR is greater-than-moderate according to the United States guideline. PH is defined as peak flow velocity of TR ≥2.9 m/s by echocardiography.
ACE, angiotensin-converting enzyme; Af, atrial fibrillation; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRTD, cardiac resynchronization therapy—ICD; FAC, fractional area change; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVDdi, indexed end-diastolic diameter of the left ventricle; MELD-XI, Model for End-stage Liver Disease excluding the international normalized ratio; MR, mitral regurgitation; PH, pulmonary hypertension; RAAi, indexed right atrial area; RVD, right ventricular diameter; RVEDA/ESA, RV end-diastolic/end-systolic area; TAD, tricuspid annular diameter; TR, tricuspid regurgitation.

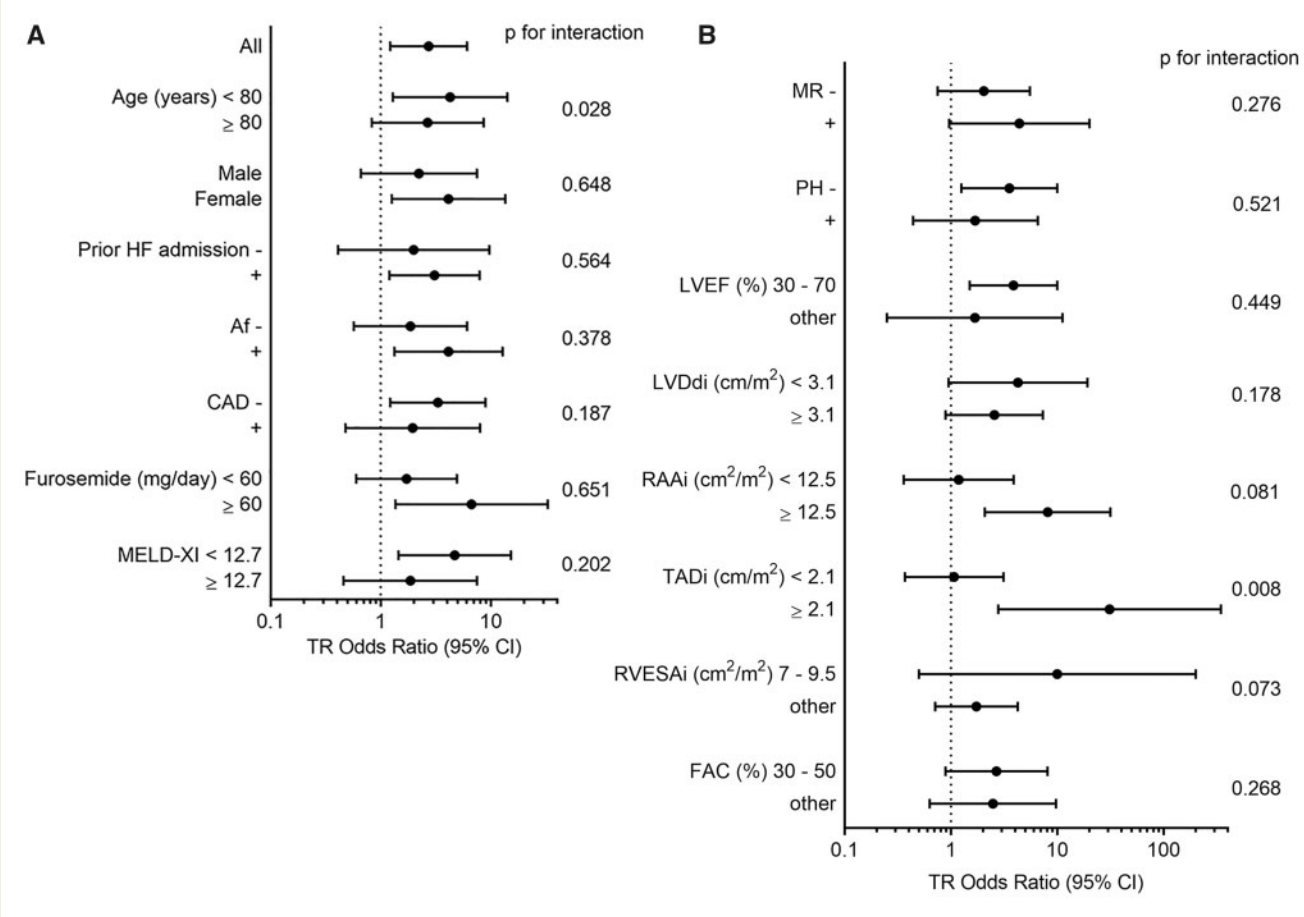


Figure 2 Specific subgroups with strong association of tricuspid regurgitation with worse heart failure outcomes. Multivariate logistic regression analyses were performed regarding heart failure readmission or cardiovascular death in a year, including age, sex, prior heart failure admission, atrial fibrillation, coronary artery disease, left ventricular ejection fraction, pulmonary hypertension, mitral regurgitation, and tricuspid regurgitation. The odds ratio plots of tricuspid regurgitation on heart failure outcomes are shown in clinical (*A*) or echocardiographic (*B*) subgroups. There was a significant subgroup interaction in age and indexed tricuspid annular diameter, and a trend of interaction in indexed right atrial area and indexed right ventricular end-systolic area. Af, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; FAC, fractional area change; HF, heart failure; LVDdi, indexed end-diastolic diameter of the left ventricle; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PH, pulmonary hypertension; RAAi, indexed right atrial area; RVESAi, indexed right ventricular end-systolic area; TADi, indexed tricuspid annular diameter; TR, tricuspid regurgitation.

Development of the echocardiographic score to predict a larger impact and burden of tricuspid regurgitation on heart failure outcomes

The discovery of specific subgroups with a large CME of TR prompted us to develop an echocardiographic predictive score for larger impact and burden of TR on HF outcomes. We considered the above results and potential indices of the RA/RV structure and function, and two indices were selected, namely TADi ≥2.1 cm/m^2 and FAC ≥30%. These were assigned one point each to develop a CME score of 0–2 points (*Table 3*). Half of the patients with TR had a CME score of 2 points (*Figure 4A*).

Next, the prediction ability of this CME score for larger TR impact was compared with that of the MELD-XI score, which is a preoperative risk marker after TR surgery.[19] Interestingly, a CME score of 2 points projected more powerful CME (the average CME 1.54) than TADi ≥2.1 cm/m^2 or FAC ≥30% alone or a MELD-XI score <12.7 in patients with Af (*Figure 4B*). A CME score of 2 points also estimated greater CME (the average CME 1.07) than the MELD-XI score in patients with MR (*Figure 4C*). There was no difference in the TR severity in these subgroups with Af or MR (Supplementary material online, *Table S3*). We found the similar prediction ability of the CME score including LVEF ≥30%.

Multivariate logistic regression analyses on HF outcomes found that there was a significant subgroup interaction in the CME scores ($P = 0.024$), and that the OR of TR with a CME score 2 (26.8, $P = 0.008$) was much higher than that with a MELD-XI score <12.7 (4.69, $P = 0.009$) (Supplementary material online, *Figure S2*).

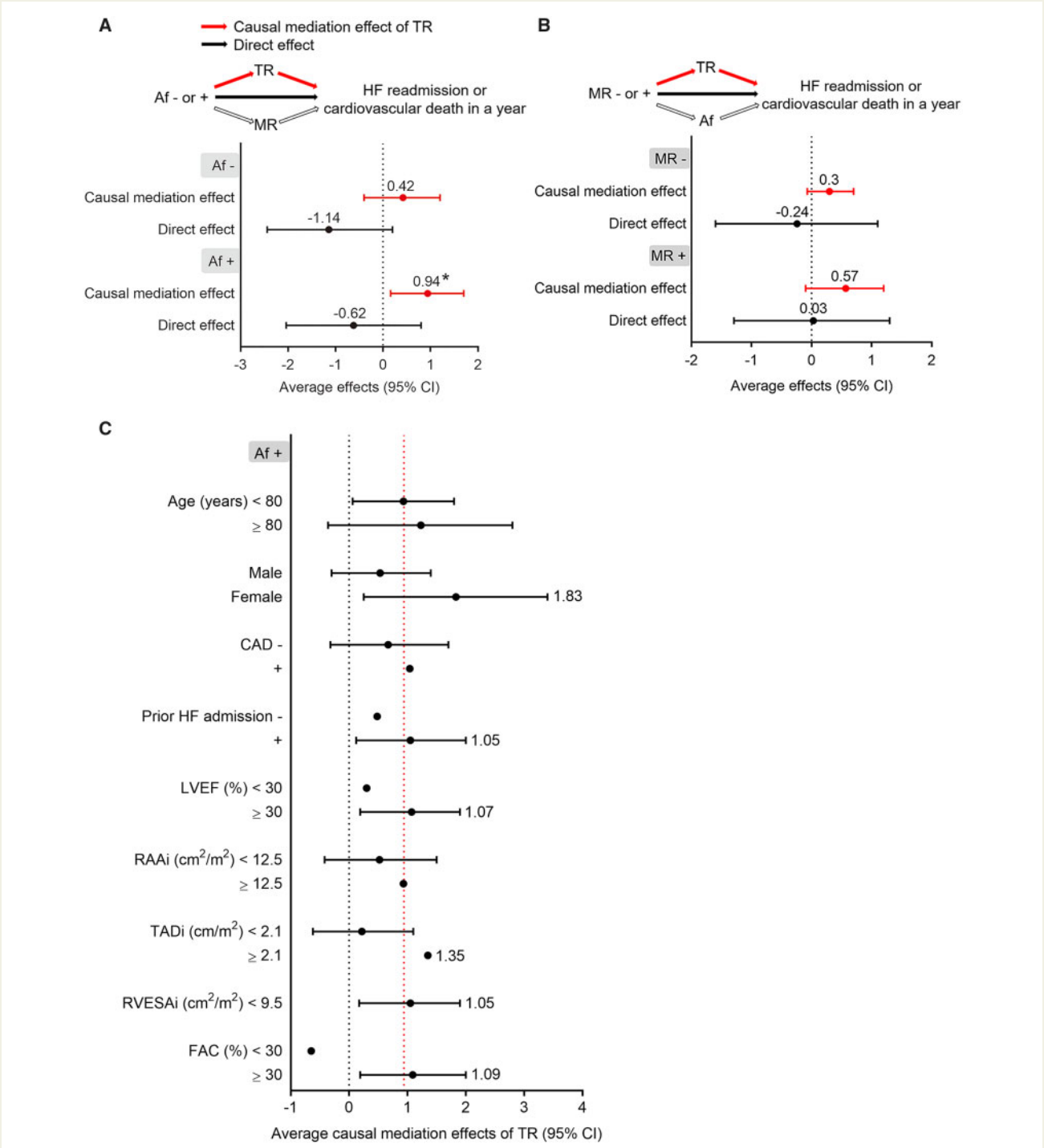


Figure 3 Identification of subgroups with large causal mediation effect of tricuspid regurgitation on heart failure outcomes. (*A and B*) Causal mediation analyses of tricuspid regurgitation. Tricuspid regurgitation was set as the main mediator of heart failure outcomes. Mitral regurgitation (*A*) or atrial fibrillation (*B*) was the alternative mediator. Age, sex, coronary artery disease, prior heart failure admission, and left ventricular ejection fraction were set as covariates. The graphs show the magnitude of the causal mediation effect of tricuspid regurgitation (causal mediation effect, red arrow and bar) and direct effect not through tricuspid regurgitation (black arrow and bar) on heart failure outcomes. The causal mediation effect was significant in patients with atrial fibrillation. *$P < 0.05$. (*C*) Subgroup disparity in the causal mediation effect in patients with atrial fibrillation. The red dotted line denotes the average causal mediation effect level (0.94) in entire patients with atrial fibrillation. The numbers next to the bar show the values of significant and/or large causal mediation effect. The causal mediation effect in indexed right ventricular end-systolic area ≥9.5 cm^2/m^2 could not be measured because there were few patients. Af, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; FAC, fractional area change; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RVESAi, indexed right ventricular end-systolic area; TADi, indexed tricuspid annular diameter; TR, tricuspid regurgitation.

Table 2. TR severity in the subgroups of causal mediation analysis

TR severity	Af			MR		
	-	+	p-value	-	+	p-value
VCW ≥ 7 mm (%)	20	38	0.172	34.8	29.2	0.79
VCW (mm)	4.0 [3.4, 5.3]	5.8 [5.0, 8.0]	0.007	5.0 [4.0, 7.9]	5.3 [5.0, 7.5]	0.439
			Subgroups in Af +			
	Age (years)			Sex		
	< 80	≥ 80	p-value	Male	Female	p-value
VCW ≥ 7 mm (%)	31.8	42.9	0.559	18.2	53.6	0.018
VCW (mm)	5.5 [5.0, 7.0]	5.8 [5.0, 8.3]	0.324	5.0 [4.0, 5.9]	7.0 [5.0, 9.3]	0.011
	CAD			Prior HF admission		
	-	+	p-value	-	+	p-value
VCW ≥ 7 mm (%)	37.8	38.5	1	18.2	43.6	0.17
VCW (mm)	6.0 [5.0, 8.0]	5.0 [5.0, 8.0]	0.397	5.0 [4.3, 5.8]	6.0 [5.0, 9.0]	0.046
	LVEF (%)			RAAi (cm^2/m^2)		
	< 30	≥ 30	p-value	< 12.5	≥ 12.5	p-value
VCW ≥ 7 mm (%)	0	41.3	0.273	12.5	42.5	0.229
VCW (mm)	5.0 [5.0, 5.5]	6.0 [5.0, 8.0]	0.474	5.0 [5.0, 5.0]	6.0 [5.0, 8.3]	0.086
	TADi (cm/m^2)			RVESAi (cm^2/m^2)		
	< 2.1	≥ 2.1	p-value	< 9.5	≥ 9.5	p-value
VCW ≥ 7 mm (%)	29.4	41.9	0.536	31	83.3	0.022
VCW (mm)	5.0 [5.0, 7.0]	6.0 [5.0, 8.5]	0.068	5.5 [5.0, 7.0]	12.8 [9.5, 14.9]	0.004
TR severity	FAC (%)					
	< 30	≥ 30	p-value			
VCW ≥ 7 mm (%)	25	40	1			
VCW (mm)	5.5 [4.6, 6.8]	6.0 [5.0, 8.0]	0.606			

Values are median [interquartile range]. VCW, vena contracta width. Other abbreviations are as in Table 1.

These findings suggest that combination of the echocardiographic indices TADi and FAC is superior to the MELD-XI score for predicting a greater TR impact irrespective of Af and MR in HF patients.

Discussion

In this retrospective HF cohort study, causal mediation analysis was performed to identify specific subgroups with a large causal impact of greater-than-moderate TR on HF readmission or CV death. First, we found that the association of TR with HF outcomes was strongest in the subgroups of females, with Af, above the cut-off value of the RAAi or TADi, or within certain ranges of the LVEF, RVESAi, or FAC. Causal mediation analysis with or without persistent Af or MR revealed that the causal impact of TR was significant in patients with Af. Furthermore, combination of TADi ≥2.1 cm/m^2 and FAC ≥30% was superior for predicting greater impact and burden of TR irrespective of Af and MR.

Here, the results showed that TADi and FAC, the indexes of RA/RV structure and RV function, respectively, exceeding the threshold values were superior to each index alone as a predictor of larger TR impact. Half of the patients with TR met these criteria in this cohort. The result implies that maintained RV systolic function to a certain degree under TA deformation best predicts the TR burden. Conversely, TR is likely to be an innocent bystander or mere marker of poor prognosis but not an effector in patients with TADi <2.1 cm/m^2 and/or FAC <30%. Importantly, the prediction ability of the developed CME score was superior to that of the existing MELD-XI score regarding a larger TR impact. Therefore, our findings will help more easily judge the TR burden in HF in clinical practice.

The cut-off value of TADi at 2.1 cm/m^2 in this study coincides with those in previous reports[15,16] in TR patients undergoing tricuspid annuloplasty with mitral valve surgery. Kim *et al.*[17] showed that larger RVESA and smaller FAC were associated with CV events in patients with isolated severe TR after surgery, and that preoperative RVESA <20 cm^2 predicted event-free survival. Although the threshold of RVESA appeared to be somewhat smaller in our study than in their report, this would be explained by the difference in the outcome and the patient population (older age and fewer percentages of previous left-sided valve surgery and Af in our study) between the studies. A recent study[32] reported that FAC was not a prognostic marker after transcatheter intervention for TR. However, their research consisted of a population with higher percentages of severe congestive HF, pacemaker/ICD implantation, and MR and larger RVEDA, and smaller FAC than those in our study. Therefore, the discrepancy regarding FAC could be explained by the difference in the patient population and the indicator of the study.

A prominent CME of TR was observed in female patients with Af. Although the mechanism of this interesting finding remains unknown, females might be more predisposed to enlarge TA but maintain FAC than males by the stress to the heart. Indexed TAD ≥2.1 cm/m^2 appeared superior to predict large TR impact than RAAi ≥12.5 cm^2/m^2 in patients with Af. This result may reflect a specific causal mechanism

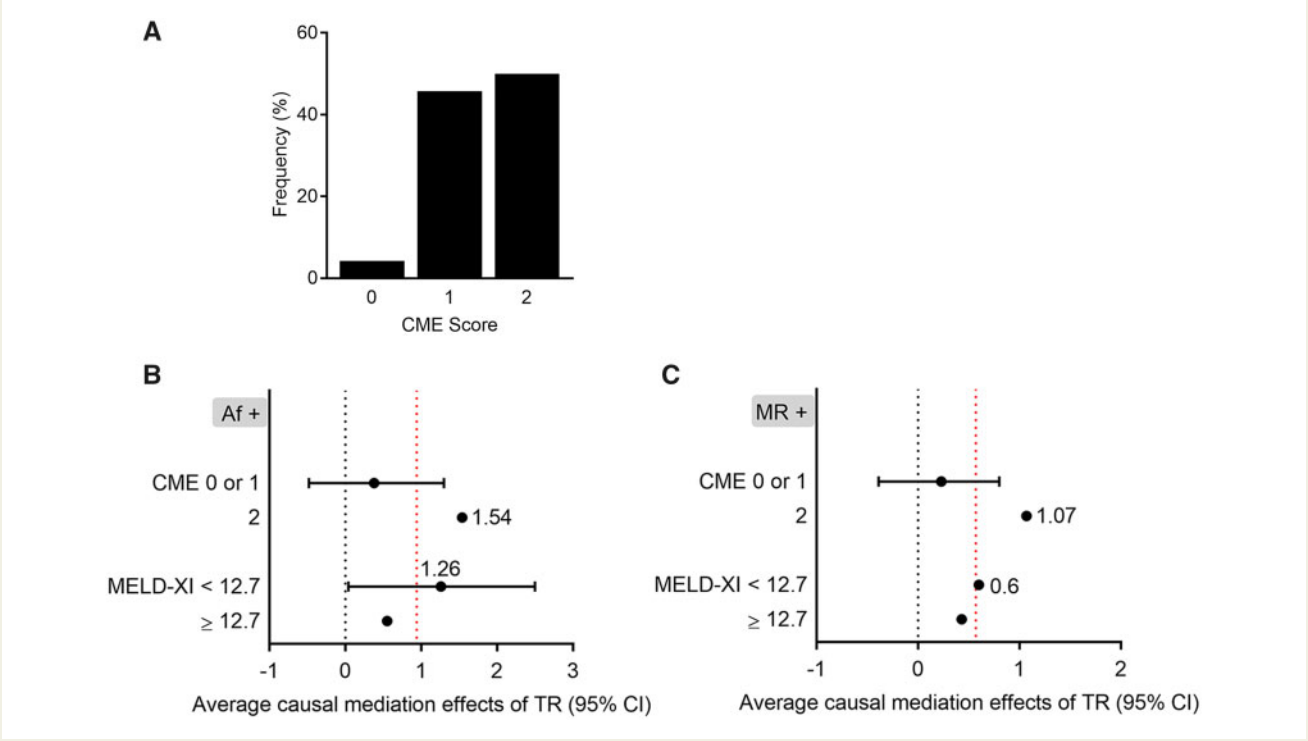


Figure 4 Prediction ability of the echocardiographic score for larger tricuspid regurgitation impact on heart failure outcomes. (*A*) Frequency of the causal mediation effect score in patients with tricuspid regurgitation. (*B and C*) The causal mediation effect of tricuspid regurgitation on heart failure outcomes by the range of the causal mediation effect score or MELD-XI score in patients with atrial fibrillation (*B*) or mitral regurgitation (*C*). The red dotted lines are the average causal mediation effect level in each group. A causal mediation effect score 2 predicted more powerful causal mediation effect than a MELD-XI score <12.7 in patients with atrial fibrillation or mitral regurgitation. CI, confidence interval; CME, causal mediation effect; MELD-XI, Model for End-stage Liver Disease excluding the international normalized ratio; TR, tricuspid regurgitation.

Table 3 The echocardiographic score to predict a large impact and burden of TR on HF outcomes

CME score	
Indices	**Point**
TADi ≥2.1 cm/m^2	1
FAC ≥30%	1
Total	0–2 points

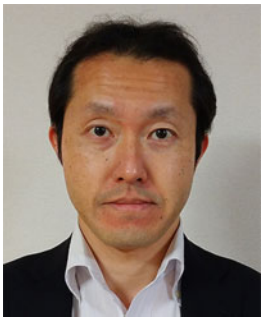
CME, causal mediation effect; FAC, fractional area change; TADi, indexed tricuspid annular diameter.

of TR in Af, namely TA and basal RV dilatation compared to leaflet tethering and ellipsoidal/spherical RV dilatation in PH-induced TR.[3,4]

There are several limitations to this study. First, this was a single-centre, retrospective study. Although the variables of age, sex, prior HF admission, CAD, and LVEF were adjusted in the causal mediation analysis, it is possible that unmeasured confounders could have biased the estimates of mediation effects. Second, as the mediation analysis provides no more than a causal inference, validation, or evaluation of our findings in another cohort or randomized controlled trial would be required in the future.

In conclusion, we performed causal mediation analysis of TR in an HF cohort and found that the causal impact of TR on HF readmission or CV death is especially significant in patients with Af, and that combining TADi ≥2.1 cm/m^2 with FAC ≥30% provides superior echocardiographic prediction for larger impact and burden of TR irrespective of Af and MR. Our findings could help select more appropriate patients and timing for therapeutic intervention for TR.

Lead author biography



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Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Conflict of interest: none declared.

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