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Clinical outcomes and progression rate of tricuspid regurgitation in patients with rheumatic mitral valve disease

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ABSTRACT

Objective A substantial proportion of patients with rheumatic heart disease (RHD) have tricuspid regurgitation (TR). This study aimed to identify the impact of functional TR on clinical outcomes and predictors of progression in a large population of patients with RHD.

Methods A total of 645 patients with RHD were enrolled, mean age of 47±12 years, 85% female. Functional TR was graded as absent, mild, moderate or severe. TR progression was defined either as worsening of TR degree from baseline to the last follow-up echocardiogram or severe TR at baseline that required surgery or died. Incidence of TR progression was estimated accounting for competing risks.

Results Functional TR was absent in 3.4%, mild in 83.7%, moderate in 8.5% and severe in 4.3%. Moderate and severe functional TR was associated with adverse outcome (HR 1.91 (95% CI 1.15 to 3.2) for moderate, and 2.30 (95% CI 1.28 to 4.13) for severe TR, after adjustment for other prognostic variables. Event-free survival rate at 3-year follow-up was 91%, 72% and 62% in patients with no or mild, moderate and severe TR, respectively. During mean follow-up of 4.1 years, TR progression occurred in 83 patients (13%) with an overall incidence of 3.7 events (95% CI 2.9 to 4.5) per 100 patient-years. In the Cox model, age (HR 1.71, 95% CI 1.34 to 2.17), New York Heart Association functional class III/IV (HR 2.57, 95% CI 1.54 to 4.30), right atrial area (HR 1.52, 95% CI 1.10 to 2.10) and right ventricular (RV) dysfunction (HR 2.02, 95% CI 1.07 to 3.84) were predictors of TR progression. By considering competing risk, the effect of RV dysfunction on TR progression risk was attenuated.

Conclusions In patients with RHD, functional TR was frequent and associated with adverse outcomes. TR may progress over time, mainly related to right-sided cardiac chambers remodelling.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Significant tricuspid regurgitation is associated with increased risk of mortality.
⇒ Tricuspid regurgitation is most often the consequence of left-sided cardiac diseases that induce right-sided chamber dilatation.

WHAT THIS STUDY ADDS

⇒ Functional tricuspid regurgitation is an independent predictor of clinical outcomes in patients with rheumatic mitral valve disease taking into account competing risks.
⇒ Tricuspid regurgitation is frequent in patients with rheumatic heart disease and progresses over time despite mitral valve intervention.
⇒ Assessing tricuspid regurgitation is essential for decision-making guidance regarding tricuspid valve intervention.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Functional tricuspid regurgitation is a progressive disease with a poor prognosis, which requires a more aggressive management to improve patient clinical outcomes. This is particularly of interest more recently when tricuspid valve interventions have been growing.

INTRODUCTION

Rheumatic heart disease (RHD) remains a major health concern, especially in low-income and middle-income countries which bear the highest disease burden. Currently, RHD affects over 40 million people with estimates of nearly 300 000 deaths globally.[1] As most RHD-related deaths occur in young adults, this number translates to a much higher burden of years of life lost and disability-adjusted life-years.[1]

RHD typically affects left-sided valves, predominantly the mitral valve which is affected in almost all RHD cases.[2] The tricuspid valve can be also affected, mainly valvular regurgitation, but it typically occurs as the result of haemodynamic consequences of the mitral valve disease with a structurally

normal valve. Functional tricuspid regurgitation (TR) implies two distinct categories related to ventricular or atrial remodelling. In ventricular TR, right ventricular (RV) enlargement leads to tricuspid annulus dilatation, which coupled with leaflet tethering secondary to apical papillary muscles displacement, and may result in valve leaflet malcoaptation with varying degrees of TR. Mitral valve disease with pulmonary hypertension is one of the most common causes of functional ventricular TR. In contrast, atrial functional TR is seen in the presence of a dilated tricuspid annulus in the context of atrial fibrillation (AF), where right atrial (RA) enlargement occurs regardless of the presence of left heart disease or pulmonary hypertension. Therefore, understanding the underlying mechanisms of functional TR is crucial in establishing the best therapeutic strategy.[3]

TR has long been the most neglected valvular disease. Historically functional TR was overlooked and considered a benign disease which would resolve after mitral valve surgery. However, TR often persists or even worsens following correction of mitral valve disease, indicating that functional TR is a progressive disease.[4 5] In the last years, there has been growing awareness of the adverse impact of TR on patient outcomes. It is established that the severity of TR is associated with long-term survival, independent of the presence of left-side valve diseases and left ventricular dysfunction.[6–8] A recent study showed that even mild TR is associated with a significant increase in mortality.[9] Thus, current guidelines recommend surgical correction of tricuspid valve in cases of moderate or more preoperative TR in the context of left-sided valve surgery.[10]

In the setting of RHD, data on TR progression are limited.[11–14] Significant TR can develop over time even after successful percutaneous mitral valvuloplasty (PMV).[13] Persistent TR despite adequate surgical and percutaneous intervention of the mitral valve disease has also been shown to be an independent predictor of an adverse outcome.[15] We previously showed that moderate or severe TR is associated with cardiovascular mortality in patients with mitral stenosis.[12] Although the prognostic impact of significant TR is well known, there is a paucity of data on the natural history of TR in a contemporary era.[16 17] In this regard, there is a need to assess TR progression for clinical decision-making, especially with the availability of transcatheter tricuspid valve interventions.

Two main challenges complicate the study of the natural history of functional TR in patients with RHD. First, the high likelihood of surgery or death related to mitral valve disease prior to TR progression requires the development of risk prediction models accounting for competing risks.[18] This provides a more accurate estimation of the risk of developing the main outcome of interest when one or more competing risks are presented. Second, the complexity of TR evaluation and lack of an accepted reference method to quantify TR severity poses difficulties in accurately assessing TR progression.[3]

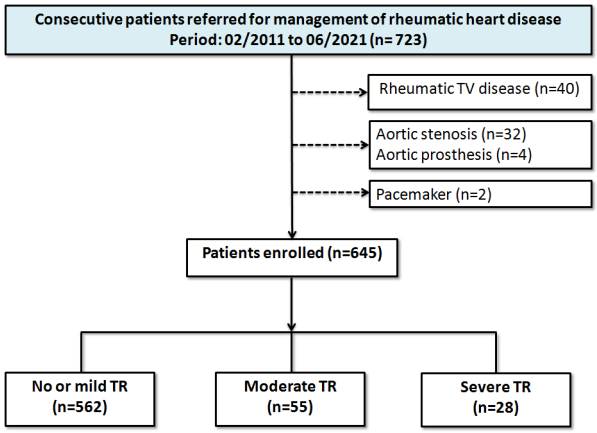

Figure 1 Flow chart of the studied population. TR, tricuspid regurgitation; TV, tricuspid valve.

Hence, the aim of this study was to (1) identify the prevalence and determinants of significant TR; (2) assess the impact of TR severity on clinical outcome and (3) determine the incidence and risk factors for TR progression in a large cohort of patients with RHD.

METHODS

Patient and public involvement statement

Patients or the public were not involved in any stage process of our research, including study design, conduct, reporting or dissemination plans.

Study population

Patients with RHD who were referred for management of heart valve disease between 2011 and 2021 were recruited prospectively for the study. The exclusion criteria were primary TR owing to rheumatic involvement of the valve, significant aortic valve disease or presence of a prosthetic aortic valve, and presence of pacemaker leads within the right heart.[19] Based on these criteria, 78 patients were excluded, mainly for primary TR (n=40) and aortic valve disease (n=36) (figure 1). At enrolment, a complete clinical evaluation was performed in all patients in the outpatient setting. Functional status was determined using the New York Heart Association (NYHA) classification and clinical features of right-sided heart failure were assessed by evaluation of jugular venous pressure, peripheral oedema and hepatomegaly.

The decision regarding mitral valve intervention including PMV, isolated mitral valve replacement isolated or combined mitral valve replacement with tricuspid valve repair was based on current guidelines,[10] at the discretion of the attending physician.

Echocardiographic study

Comprehensive transthoracic echocardiography was performed prospectively in all patients using commercially available equipment (ie, 33 and EPIQ 7, Philips Medical Systems, Andover, Massachusetts, USA). The presence and severity of mitral valve disease were assessed based on morphology, colour flow imaging and continuous wave

Table 1 Baseline clinical characteristics of study population, stratified by TR severity

	No or mild TR (n=562)	Moderate TR (n=55)	Severe TR (n=28)	P value
Clinical data*				
Age (years)	46.3±12.1	52.9±11.3	59.6±11.7	<0.001
Female	476 (85)	46 (84)	25 (89)	0.779
Body surface area (m^2)	1.70±0.2	1.69±0.2	1.62±0.1	0.106
Body mass index (kg/m^2)	26.5±5.5	27.3±5.7	26.4±5.5	0.626
NYHA classes III–IV	197 (35)	22 (40)	17 (61)	0.022
Chest pain	242 (43)	18 (32)	4 (14)	0.003
Right-sided heart failure	112 (20)	18 (33)	18 (64)	<0.001
Atrial fibrillation	152 (27)	32 (58)	21 (75)	<0.001
Previous MV intervention†	167 (30)	20 (36)	15 (54)	0.024
Ischaemic cerebrovascular events‡	107 (19)	11 (20)	6 (22)	0.903
Comorbidities				
Diabetes	15 (3)	3 (6)	1 (4)	0.303
Hypertension	140 (25)	15 (28)	12 (42)	0.132
Medications				
Diuretics	371 (66)	43 (78)	27 (96)	0.001
β-Blockers	416 (74)	49 (89)	21 (75)	0.031
ACE inhibitors	96 (17)	10 (17)	9 (36)	0.046
Angiotensin receptor blockers	57 (10)	8 (15)	4 (15)	0.440
Penicillin benzathine use	136 (24)	12 (22)	4 (14)	0.459
Anticoagulation therapy	202 (36)	31 (57)	19 (68)	<0.001
Heart rate (bpm)	69.2±12.7	72.7±15.9	73.4±21.5	0.065
Systolic blood pressure (mm Hg)	116.5±17.2	118.9±14.7	117.2±16.3	0.605
Diastolic blood pressure (mm Hg)	75.1±11.2	75.6±9.5	75.4±11.8	0.927

*Data are expressed as the mean value±SD or absolute numbers (percentage).
†Surgical commissurotomy or percutaneous valvuloplasty. Twenty-one patients underwent both procedures.
‡Stroke or transient ischaemic attack at baseline.
MV, mitral valve; NYHA, New York Heart Association; TR, tricuspid regurgitation.

Doppler signals, as recommended.[20] Net atrioventricular compliance (C_n) was also determined noninvasively using Doppler echocardiography.[12 21]

After careful tricuspid valve examination excluding rheumatic involvement, functional TR was graded according to American Society of Echocardiography guidelines.[22] Standard practice at our institution is to classify the TR severity as absent or trivial, mild, moderate and severe using an integrative approach considering multiple qualitative and semiquantitative parameters, including tricuspid inflow, colour flow regurgitant jet area, continuous wave shape and density of regurgitant jet, hepatic vein flow reversal, PISA radius and enlargement of cardiac chambers.[22]

The right ventricle was imaged from multiple views, including RV-focused apical four-chamber views. Standard parameters of RV function were measured including fractional area change, peak systolic velocity at the tricuspid annulus using tissue Doppler imaging, tricuspid annular plane systolic excursion and RV myocardial performance index.[20] Systolic pulmonary artery pressure (SPAP) was calculated using the TR jet velocity and an estimation of RA pressure based on inferior vena cava size and collapsibility. RA size was quantified by measuring atrial area at the apical four-chamber view. The tricuspid annular diameter was measured in end-diastole at the apical four-chamber view. All results were based on the average of measurements from three cardiac cycles for patients in sinus rhythm and five cardiac cycles for patients in AF.

Definition of TR progression

Progression of TR was defined as the composite of the following: (1) worsening of the degree of TR from mild to moderate or moderate to severe consistently at follow-up echocardiograms, being at least moderate at the last echocardiographic evaluation; (2) severe TR at baseline that underwent TR repair at the time of mitral valve replacement and (3) severe TR in patients who died from cardiac cause. Patients with an increase in TR severity in

Table 2 Baseline echocardiographic characteristics of study population, stratified by TR severity

Echocardiographic data		No or mild TR (n=562)	Moderate TR (n=55)	Severe TR (n=28)	P value
LVDd (mm)		48.6±6.0	48.6±6.3	43.0±6.1	<0.001
LVSd (mm)		31.8±5.1	32.0±7.2	29.5±6.2	0.088
LVEF (%)		62.8±7.5	59.8±8.7	57.0±8.7	<0.001
LA dimension (mm)		49.5±7.1	53.2±8.1	53.6±6.2	<0.001
LAV index (mL/m^2)		60.2±25.2	68.2±31.4	66.7±26.8	0.053
Peak gradient (mm Hg)		17.9±6.9	19.5±7.3	16.7±9.5	0.193
Mean gradient (mm Hg)		9.8±4.8	10.7±4.9	8.7±5.5	0.215
Mitral valve area (cm^2)*		1.2±0.4	1.1±0.3	0.99±0.4	0.017
Leaflets displacement (mm)		14.8±2.7	13.8±3.0	12.8±2.9	0.001
C_n (mL/mm Hg)		5.2±1.9	4.5±1.6	5.1±1.6	0.031
Mitral regurgitation	Absent	71 (13)	6 (11)	1 (4)	0.028
	Mild	447 (80)	40 (73)	26 (93)	
	Moderate	42 (8)	7 (13)	1 (4)	
	Severe	2 (0.4)	2 (4)	0	
RV function parameters					
RV basal diameter (mm)		38.2±5.2	43.3±6.8	52.3±10.4	<0.001
Impaired RV contractility†		118 (21)	31 (57)	25 (89)	<0.001
Systolic annular velocity (cm/s)‡		10.6±2.1	9.8±2.5	8.4±1.8	<0.001
Tricuspid annular diameter (mm)		31.9±6.1	37.8±5.4	44.8±9.8	<0.001
Tricuspid annular index (mm/m^2)		18.6±3.5	22.2±4.1	27.6±5.0	<0.001
Tricuspid annular motion (mm)		18.2±4.2	15.7±3.1	14.6±3.7	<0.001
RV end-diastolic area (cm^2)		17.2±3.8	19.7±5.7	27.9±12.0	<0.001
RV end-systolic area (cm^2)		9.1±3.0	11.7±5.5	16.0±7.6	<0.001
RV fractional area change (%)		47.5±10.1	42.6±13.4	43.7±8.6	0.004
RV myocardial performance index		0.34±0.17	0.42±0.20	0.35±0.12	0.014
RA area (cm^2)		16.0±4.8	21.6±5.9	31.1±13.2	<0.001
SPAP (mm Hg)		41.7±15.5	56.4±24.1	43.4±15.5	<0.001
Estimated RA pressure (mm Hg)		4.5±3.7	6.8±4.6	13.6±3.1	<0.001

Data are expressed as the mean value±SD or absolute numbers (percentage).
*Mitral valve area by planimetry.
†RV contractility was assessed qualitatively by multiple views.
‡Peak systolic velocity at the tricuspid annulus.
C_n, net atrioventricular compliance; LA, left atrium; LAV, left atrial volume; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVSd, left ventricular end-systolic diameter; MR, mitral regurgitation; RA, right atrium; RV, right ventricular; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

only one examination but a follow-up echocardiogram unchanged were not considered to have any progression.

Clinical outcomes

Adverse outcome was a composite of cardiovascular-related death and need for mitral valve replacement. Cardiovascular mortality was defined as death due to stroke, heart failure or sudden death. Follow-up data were obtained from follow-up appointments every 4 months or more often according to the patients' clinical status on an outpatient basis. Additional information was also obtained by contacting family members or telephone interviews of the patients. Patients who underwent surgery for mitral valve replacement were censored at the time of the procedure.

Statistical analysis

Categorical variables were expressed as numbers and percentages whereas continuous data were expressed as mean±SD. Clinical characteristics were compared across the degree of TR at baseline using the χ^2 test, one-way analysis of variance or Kruskal-Wallis tests, according to the pattern of variable distributions.

Table 3 Clinical and echocardiographic characteristics associated with more severe tricuspid regurgitation in patients with RHD

	Unadjusted		Multivariable adjustment for age, female sex, atrial fibrillation, SPAP, LVEF and RA area		Multivariable adjustment for age, female sex, atrial fibrillation, SPAP, LVEF, RA area and RV dysfunction*	
At baseline	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age, years	1.062 (1.041 to 1.084)	<0.001	1.049 (1.017 to 1.081)	0.002	1.061 (1.029 to 1.094)	<0.001
Female sex	1.069 (0.556 to 2.055)	0.841	1.706 (0.701 to 4.151)	0.239	1.986 (0.795 to 4.964)	0.142
Atrial fibrillation	4.755 (2.925 to 7.728)	<0.001	1.650 (0.717 to 3.797)	0.239	1.042 (0.425 to 2.552)	0.929
SPAP (mm Hg)	1.029 (1.017 to 1.042)	<0.001	1.051 (1.030 to 1.071)	<0.001	1.041 (1.021 to 1.061)	<0.001
LVEF (%)	0.943 (0.918 to 0.969)	<0.001	0.995 (0.995 to 1.0376)	0.796	1.008 (0.965 to 1.053)	0.728
RA area (cm^2)	1.238 (1.173 to 1.308)	<0.001	1.196 (1.117 to 1.281)	<0.001	1.188 (1.115 to 1.265)	<0.001
RV dysfunction*	7.793 (4.683 to 12.967)	<0.001			2.927 (1.401 to 6.115)	0.004

Model without RV dysfunction: C-statistic of 0.878 (95% CI 0.836 to 0.920).
Model with RV dysfunction: C-statistic of 0.888 (95% CI 0.844 to 0.932).
*RV function was assessed using a combination of parameters and categorised in normal or impaired function.
LVEF, left ventricular ejection fraction; RA, right atrium; RHD, rheumatic heart disease; RV, right ventricular; SPAP, systolic pulmonary artery pressure.

A Cox proportional hazards regression model analysing the association of TR with adverse outcomes was adjusted for age, NYHA functional class, AF, left ventricular (LV) ejection fraction, pulmonary artery pressure, RV dysfunction and C_n. PMV performed at a short time from enrolment was included in the model as covariate. To avoid redundant predictors, variables were checked for collinearity and obviously interdependent covariates were not used simultaneously in the multivariable model.

Two regression models were used to identify the predictors of TR progression during the follow-up time. The first was the Cox proportional hazards model in which patients TR progression was the primary event and patients who died or underwent mitral valve replacement with or without tricuspid valve repair were censored. The second model was the Fine-Gray competing risk model in which TR progression was the primary event and deaths and surgery were the competing risks.[23] Both models were adjusted for age, NYHA functional class, AF, LV ejection fraction, pulmonary artery pressure, RV dysfunction, RA area and mitral valvuloplasty at enrolment. The estimated regression coefficients for each variable were compared between the two models to examine whether there were differences in the direction of their association with the rate of TR progression (derived from the Cox model) versus its incidence (derived from the Fine-Gray model).[23]

Multiple imputation techniques were used to explore the robustness of inference to missing data. For these analyses, we assumed data are missing at random and performed 200 multiple imputations, which were generated via the multivariate imputation by chained equations procedure. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, V.22.0 (SPSS) and R for Statistical Computing V.3.6.3 (R Foundation, Vienna, Austria).

RESULTS

Baseline characteristics

Among 723 initially selected, 40 patients had primary rheumatic involvement of the valve, 36 presented associated moderate or severe aortic stenosis and 2 with a pacing wire (figure 1). In the 645 patients enrolled, TR was absent in 22 (3.4%), mild in 540 (83.7%), moderate in 55 (8.5%) and severe in 28 (4.3%). Baseline clinical characteristics of the patient population by TR degree are displayed in table 1. The mean age was 47±12 years with females representing 85% of the cohort. At enrolment, 236 patients (36%) were in NYHA III/IV and 148 patients (23%) presented with right-sided heart failure. Patients with higher TR grade were older, had worse functional class and higher prevalence of AF compared with no or mild TR.

Baseline echocardiographic characteristics stratified by TR degree are displayed in table 2. Left ventricular function was reduced across the spectrum of TR severity. As expected, patients with moderate or severe TR had more RV dysfunction than those with mild TR.

Clinical and echocardiographic characteristics associated with more severe TR are presented in table 3. In the multivariable model, age, pulmonary artery pressure and RA area were independent factors associated with TR severity with C-statistic of 0.878 (95% CI 0.836 to 0.920). In the final model adding RV dysfunction, it remained independently associated with significant TR (adjusted OR of 2.93 (95% CI 1.40 to 6.12) with C-statistic of 0.888 (95% CI 0.844 to 0.932). Although the presence of AF was a strong predictor of TR severity with an unadjusted OR of 4.76 (95% CI 2.93 to 7.73), it did not remain in the model adjusted by age, pulmonary artery pressure and RA area.

Table 4 Univariable and multivariable Cox proportional hazard models assessing the impact of TR severity on adverse outcomes

At baseline	No events* (n=426)	Cardiovascular events (n=185)	Unadjusted		Multivariable adjustment for age, NYHA class, AF, LVEF, SPAP, RV dysfunction, C_n and PMV intervention		Multivariable adjustment for age, NYHA class, AF, LVEF, SPAP, RV dysfunction, C_n, PMV intervention and TR degree	
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	45.3±11.8	52.5±12.0	1.045 (1.033 to 1.058)	<0.001	1.037 (1.022 to 1.051)	<0.001	1.031 (1.015 to 1.046)	<0.001
NYHA III–IV	140 (33)	85 (46)	1.959 (1.461 to 2.628)	<0.001	2.174 (1.529 to 3.092)	<0.001	2.102 (1.479 to 2.987)	<0.001
AF	115 (27)	80 (43)	1.983 (1.474 to 2.666)	<0.001	…	…	…	…
LVEF (%)	62.8±7.3	60.8±8.5	0.971 (0.955 to 0.988)	0.001	0.969 (0.949 to 0.989)	0.002	0.973 (0.953 to 0.993)	0.010
SPAP (mm Hg)	42.2±16.8	45.7±18.0	1.010 (1.002 to 1.018)	0.010	1.010 (0.998 to 1.021)	0.095	…	…
RV dysfunction	102 (24)	70 (38)	1.837 (1.357 to 2.485)	<0.001	…	…	…	…
C_n (mL/mm Hg)	5.3±1.9	4.8±1.7	0.869 (0.789 to 0.957)	0.004	0.880 (0.780 to 0.993)	0.038	0.850 (0.766 to 0.944)	0.002
PMV†	270 (63)	93 (50)	0.576 (0.431 to 0.769)	<0.001	0.438 (0.302 to 0.634)	<0.001	0.441 (0.305 to 0.637)	<0.001
TR degrees								
No or mild TR	391 (92)	141 (76)	Reference		Reference		Reference	
Moderate TR	27 (6)	24 (13)	2.132 (1.382 to 3.290)	0.001			1.908 (1.149 to 3.168)	0.013
Severe TR	8 (2)	20 (11)	3.650 (2.283 to 5.834)	<0.001			2.298 (1.279 to 4.132)	0.005

*Five patients (0.8%) died from non-cardiac causes, and in 29 patients (4.5%), follow-up data were not obtained.
†PMV performed short-term after enrolment (median of 2.3 months).
AF, atrial fibrillation; C_n, net atrioventricular compliance; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PMV, percutaneous mitral valvuloplasty; RA, right atrium; RV, right ventricular; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

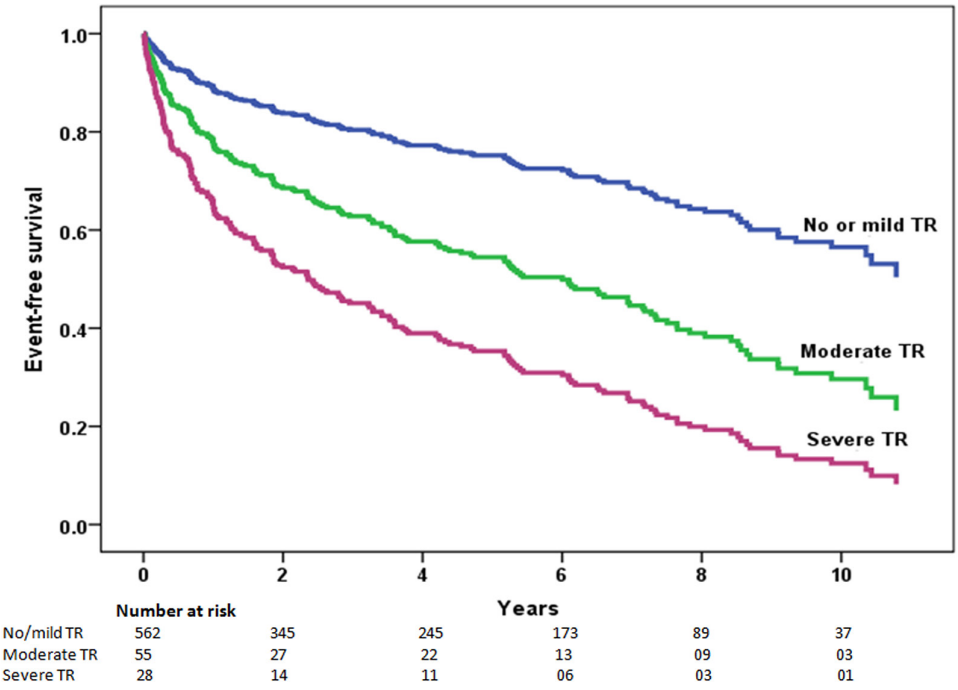

Figure 2 Event-free survival rate according to tricuspid regurgitation (TR) degree at enrolment in patients with rheumatic mitral valve disease.

Impact of TR on clinical outcomes

During mean follow-up of 4.1 years (median 3.4, IQR 1.0–6.6 years), 40 patients (6.2%) died being 35 cardiovascular and 5 non-cardiovascular deaths. In addition, 150 patients underwent surgery for mitral valve replacement in which 24 received concomitant tricuspid valve repair during the mitral valve surgery. Overall, 185 patients had adverse events whereas 29 patients were lost to follow-up and were excluded from this analysis.

The predictors of adverse outcome are shown in table 4. After adjusting for age, symptoms, left ventricular ejection fraction and net atrioventricular compliance (C_n), moderate or severe TR was associated with adverse outcome with HR for moderate TR of 1.91 (95% CI 1.15 to 3.17) and 2.30 (95% CI 1.28 to 4.13) for severe TR compared with no or mild TR. PMV performed short-term after enrolment (within 2 months) was associated with better event-free survival.

Event-free survival rates decreased with increasing severity of functional TR, with survival rate at 3-year follow-up of 91%, 72% and 62% in patients with no or mild, moderate and severe TR, respectively (figure 2).

Predictors of progression of TR

During the follow-up period, TR progression occurred in 83 patients (12.9%) of the evaluated patients with an overall incidence of progression rate of 3.7 events (95% CI 2.9 to 4.5) per 100 patient-years. Of these, 45 patients had progressed from none/mild to moderate TR and 18 had progressed from moderate to severe TR. Of the 28 patients with severe TR at baseline, 10 patients (1.6%) died and other 10 (1.6%) underwent tricuspid valve repair surgery concomitant with mitral valve replacement during follow-up.

The cumulative incidence of TR progression over 10 years was 34.3% (95% CI 25.8% to 41.9%) when using the Kaplan-Meier model and was 24.8% (CI 19.5% to 30.5%) when using the Fine-Gray model (figure 3). Predictors of TR progression were assessed in two multivariable models and the results were compared controlling for AF, pulmonary artery pressure and RV dysfunction (table 5). The HRs of each predictor comparing the Cox and the Fine-Gray models are shown in figure 4.

In the Cox model, age (HR 1.708, 95% CI 1.343 to 2.172), NYHA functional class III/IV (HR 2.572, 95% CI 1.540 to 4.298), RA area (HR 1.521, 95% CI 1.101 to 2.102) and presence of RV dysfunction (HR 2.024, 95% CI 1.068 to 3.836) were independently predictive of TR progression. In the Fine-Gray model considering competing risks, the effect of all covariates on the hazard of TR progression was similar (figure 4) with attenuated effect of RV dysfunction on TR progression risk (HR 1.694; 95% CI 0.903 to 3.179).

DISCUSSION

This study investigated the impact of TR on clinical outcomes and predictors of progression in a contemporary population with rheumatic mitral valve disease. The key findings include: (1) the prevalence of significant functional TR was 12.9% in this large cohort; (2) determinants of TR severity were age, RA area, SPAP and RV dysfunction; (3) an association between either moderate or severe TR with clinical outcomes, after adjustment for well-established prognostic variables; (4)

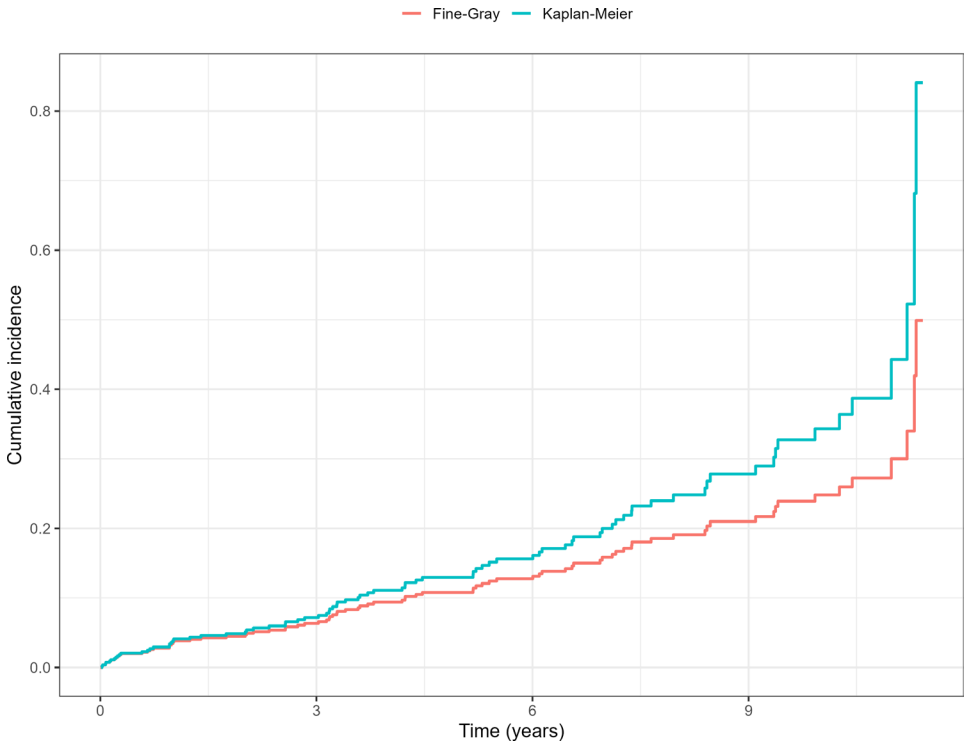

Figure 3 The cumulative incidence of tricuspid regurgitation progression over 10 years by the Cox model and the Fine-Gray model.

TR progresses over time with an incidence of progression of 3.7 events per 100 patient-years and (5) predictors of TR progression were age, NYHA functional class and RA area after considering death and mitral valve surgery as competing risks. We believe this study provides important information regarding three aspects of functional TR in the setting of RHD: prevalence, prognostic impact and predictors of progression.

Determinants of functional TR in RHD

Significant functional TR represents a poor prognostic factor independent of RV function.[13 14 21 24] It is usually the consequence of left-sided cardiac diseases that induce RV dilatation and dysfunction, and also resulted from RA enlargement and consequent tricuspid annular dilatation, mainly in patients with rheumatic mitral stenosis.[6 16] Our study confirms the association between right-sided chamber dilatation and significant TR. Despite AF being a known risk factor for severe TR, RA enlargement may be a downstream reflection of atrial myopathy, which remained in the model after adjustment for the effects of AF.

Prognostic value of functional TR

The presence of significant TR has been associated with an increase in morbidity and mortality.[5 12 24] Nath *et al*

Table 5 Multivariable regression models assessing risk factors for tricuspid regurgitation progression in patients with RHD

	Cox regression model			Fine-Gray model*		
Variables	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age (years)	1.708	1.343 to 2.172	<0.001	1.417	1.108 to 1.813	0.006
NYHA functional class III/IV	2.572	1.540 to 4.298	<0.001	1.894	1.165 to 3.079	0.010
Atrial fibrillation	1.215	0.633 to 2.330	0.558	1.014	0.530 to 1.940	0.970
SPAP (mm Hg)	1.044	0.900 to 1.210	0.572	1.003	0.874 to 1.151	0.970
PMV	1.322	0.744 to 2.347	0.341	1.758	1.007 to 3.072	0.047
RA area (cm^2)	1.521	1.101 to 2.102	0.011	1.662	1.290 to 2.141	<0.001
RV systolic annular velocity (cm/s)	0.930	0.808 to 1.070	0.309	0.899	0.773 to 1.046	0.170
RV dysfunction	2.024	1.068 to 3.836	0.031	1.694	0.903 to 3.179	0.100

*Fine-Gray model dealing with deaths and surgery alternatively as competing risks.
NYHA, New York Heart Association; PMV, percutaneous mitral valvuloplasty; RA, right atrium; RHD, rheumatic heart disease; RV, right ventricular; SPAP, systolic pulmonary artery pressure.

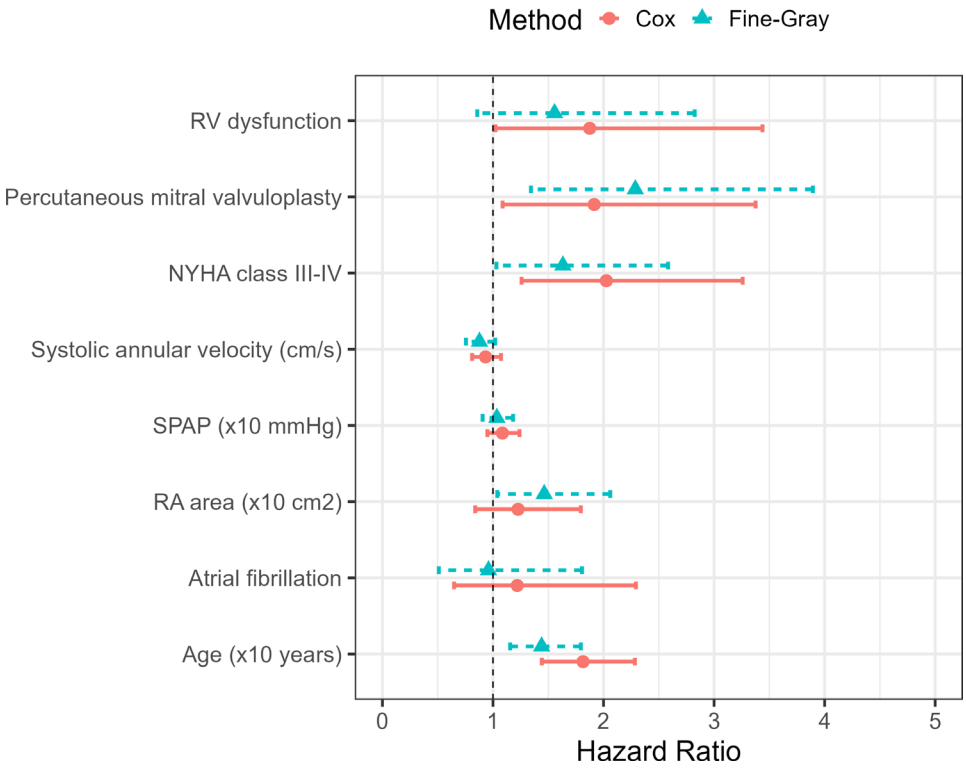

Figure 4 Multivariable predictive models for TR progression in patients with rheumatic mitral valve disease. Cox proportional hazards model considering TR progression as the primary event and the Fine-Gray model analysing surgery and death as a competing event. NYHA, New York Heart Association; RA, right atrial; RV, right ventricular; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

in a large study encompassing more than 5200 patients described that mortality increased with increasing severity of TR with a 1-year survival of 63.9%.[25] A meta-analysis of 32 601 patients with a mean follow-up of 3.2 years demonstrated that moderate and severe functional TR was associated with a twofold increased mortality risk compared with no or mild functional TR (RR 1.95, 95% CI 1.75 to 2.17), independent of pulmonary pressure and RV failure.[26] We obtained a similar association between adverse outcomes and moderate or severe TR, with an HR of 1.9 e 2.3, respectively.

Functional TR progression

There is a paucity of data on the risk factors for progression TR in patients with RHD.[15 27 28] In a previous retrospective study using a database of the echocardiography laboratory, the progression rate was 18.8%, which is similar to our study. However, this study included a heterogeneous population with associated left-sided cardiac comorbidities that may influence TR progression.[27] In our study, we specifically included only patients with RHD and excluded all those with primary causes for TR to prevent confounding factors that may influence the progression of TR over time.

AF has also been reported to be an important risk factor for TR progression.[29] In this context, RA enlargement and tricuspid annulus remodelling lead to atrial functional TR, which can occur independent of the presence of left heart disease or pulmonary hypertension. In our study, RA dilation was an independent factor for the development of significant TR, and pulmonary artery pressure has not a significant role in predicting the progression of TR.[3] The analysis of a previous study showed that a small number of patients with AF and normal pulmonary artery pressure remain at substantial risk for TR progression.[8] In another study, reduced tricuspid annulus plane systolic excursion and tricuspid annulus dilation were independently associated with progression to significant TR in a large retrospective study with 1000 patients[30]

Previous studies seeking to identify TR progression have generally identified possible associated factors in a cross-sectional manner. Our study, in addition to being based on a large cohort of patients, is a prospective study evaluating patients with rheumatic mitral valve disease to determine the rate of TR progression and its prognostic impact, hence a more accurate temporal trend. Our study has also assessed the predictors involved in progression of TR, taking into account competing risks. Typically, patients with rheumatic mitral valve disease and significant TR usually are referred for surgery or expire prior to intervention which makes assessment of TR progress challenging. Therefore, our study accounts for competing risks to conduct an appropriated time-to-event analysis on incidence of TR progression in patients with RHD.

Study limitations

This study has some limitations. First, the measurement of the tricuspid annulus by two-dimensional echocardiogram may not accurately reflect the extent of annulus remodelling which would impact on TR progression. Changes in RV geometry potentially cause displacement of the papillary muscles which result in leaflet tethering, which may also have a significant impact on development of TR. Second, there is currently a new classification of the degree of TR into massive and torrential,[31] which was not measured in our study. The new classification has a prognostic impact in terms of mortality and hospitalisation for heart failure and could have contributed to the identification of other parameters of TR progression. Third, quantitative parameters to assess TR severity were not measured, including vena contracta width and effective regurgitant orifice area. Finally this is a single-centre study which requires external validation of the results.

CONCLUSIONS

In patients with RHD, functional TR was frequent and associated with adverse outcomes, independent of symptoms and other well-established prognostic parameters. TR may progress over time, predicted by age, NYHA functional class and right-sided cardiac chambers remodelling. By considering competing risks, the effect of RV dysfunction on TR progression risk was attenuated. Assessing of functional TR is essential in a patient with RHD for risk stratification and decisions regarding tricuspid valve intervention.

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