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Tricuspid regurgitation and long-term clinical outcomes

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Aims Tricuspid regurgitation (TR) is a frequent echocardiographic finding; however, its effect on outcome is unclear. The objectives of current study were to evaluate the impact of TR severity on heart failure hospitalization and mortality.

Methods and results We retrospectively reviewed consecutive echocardiograms performed between 2011 and 2016 at the Tel-Aviv Medical Center. TR severity was determined using semi-quantitative approach including colour jet area, vena contracta width, density of continuous Doppler jet, hepatic vein flow pattern, trans-tricuspid inflow pattern, annular diameter, right ventricle, and right atrial size. Major comorbidities, re-admissions and all-cause mortality were extracted from the electronic health records. The final analysis included 33 305 patients with median follow-up period of 3.34 years (interquartile range 2.11–4.54). TR (≥mild) was present in 31% of our cohort. One-year mortality rates were 7.7% for patients with no/trivial TR, 16.8% for patients with mild TR, 29.5% for moderate TR, and 45.6% for patients with severe TR ($P < 0.001$). Univariate and multivariate analyses demonstrated a positive correlation between TR severity and overall mortality and rates of heart failure re-admission after adjustment for potential confounders. The proportional hazards method for overall mortality showed that patients with moderate [hazard ratio (HR) 1.15, 95% confidence interval (CI) 1.02–1.3, $P = 0.024$] and severe TR (HR 1.43, 95% CI 1.08–1.88, $P = 0.011$) had a worse prognosis than those with no or minimal TR.

Conclusions The presence of any degree of TR is associated with adverse clinical outcome. At least moderate TR is independently associated with increased mortality.

Keywords tricuspid regurgitation • echocardiography • prognosis

Introduction

Tricuspid regurgitation (TR) is a common echocardiographic finding that is present in 70–90% of the general population.[1] Severe TR was shown to be associated with adverse outcome in a large heterogeneous group of patients,[2] leading to the assumption that tricuspid valve repair or replacement may lead to survival benefit.[3,4] However, guidelines regarding the management of TR remain vague due to the paucity of outcome studies and their contradictory results.[3,5]

It has traditionally been believed that TR should be managed medically, and that functional TR improves with resolution of the underlying cause.[6] Nevertheless, recent evidence shows that prolonged right ventricular (RV) volume overload due to chronic TR may result in irreversible RV myocardial damage.[2,7]

In this study, we evaluate the association between TR severity and mortality and the rates of heart failure hospitalization, after adjustment for clinical and echocardiographic parameters. We hypothesized that moderate or greater degree of TR adversely impacts

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survival and heart failure re-admissions, independent of potential confounders.

Methods

Study design and setting

This is a retrospective analysis of consecutive echocardiographic examinations which were acquired between March 2011 and June 2016 at the Tel-Aviv Medical Center. Outcomes including heart failure hospitalization and all-cause mortality were analysed from the time of echocardiographic diagnosis until death or last follow-up during June 2017. Date of death was ascertained using the national health database, ensuring data accuracy. Congestive heart failure was diagnosed based on Framingham criteria.[8] Heart failure hospitalization was considered as an admission for heart failure during follow-up. The study was reviewed and approved by the Institutional Review Board in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, with a waiver of informed consent.

Study population

The study population consisted of examinees who underwent echocardiographic examinations at the Tel-Aviv Medical Center. We retrospectively reviewed 66 393 consecutive echocardiographic examinations which were acquired between March 2011 and June 2016. Excluded were repeat examinations of the same patient ($n = 25\ 674$). Also excluded were 7414 examinations in which the severity of the TR was not properly evaluated or adequately reported. The final cohort consisted of 33 305 patients and was composed of two groups: the first group ($n = 20\ 279$, 60.9%) underwent echocardiographic evaluation during hospitalization; the second group ($n = 13\ 026$, 39.1%) underwent ambulatory echocardiography as outpatients. Each of the two groups displayed distinct characteristics, and clinical data were not reported in the majority of ambulatory patients. In order to avoid bias, we performed analyses for each group separately as well as for the combined cohort.

Echocardiography and evaluation of TR severity

Echocardiography was performed in a standard manner, using the same equipment (iE33, Philips Medical Systems, Bothell, WA, USA). TR severity was determined using an integrative, semi-quantitative approach as recommended by the American Society of Echocardiography.[7] The severity of valve regurgitation was first assessed by evaluating specific signs including colour jet area (thin small central vs. large >50% jet area), vena contracta width (<0.2 cm or ≥0.7 cm), density of continuous Doppler jet (faint or dense and triangular), hepatic vein flow pattern (systolic dominant vs. systolic reversal), trans-tricuspid inflow pattern (A-wave dominant or high-velocity *E*-wave dominant), annular diameter (normal vs. dilated annulus with lack of valve coaptation), and RV and right atrial (RA) size (normal vs. dilated). If all of the signs and indices were concordant, we defined TR as ≤mild or severe. In the ≤mild group, we first discriminated patients with no TR, or with minimal TR (jet area ≤1.0 cm^2). The rest of the patients within this group were defined as mild TR. If the signs or values of the qualitative or semi-quantitative parameters were in the intermediate range between mild and severe, we defined TR as moderate.[7] Haemodynamic assessment estimated RA pressure using the inferior vena cava to calculate the systolic pulmonary artery pressure.

All volumetric measurements were divided by the body surface area and reported as millilitre/square metre (mL/m^2). Pulsed-wave Doppler was performed in the apical four-chamber view to obtain mitral inflow velocities to assess left ventricle (LV) filling. Measurements of mitral inflow included the peak early filling (*E* wave) and late diastolic filling (*A* wave) velocities, the *E*/*A* ratio, and deceleration time of early filling velocity. Early diastolic mitral annular velocities (e') were measured in the apical four-chamber view. The e' was measured from septal and lateral annulus in all patients. The ratio of peak *E* to peak e' (septal, lateral, and average) was calculated (mitral *E*/e ratio) from the average of at least three cardiac cycles. In patients with atrial fibrillation, all measurements were averages of ≥7 cardiac cycles. Ejection fraction was calculated by the Quinones method, or Simpson's method in patients with segmental wall abnormalities. LV diameters, inter-ventricular septal and posterior wall width, LV mass, and relative wall thickness were measured as recommended. Forward stroke volume was calculated from left ventricular outflow tract with subsequent calculation of cardiac output index. RV function was evaluated by tricuspid annular plane systolic excursion (TAPSE). TAPSE is a method to measure the distance of systolic excursion of the RV annular segment along its longitudinal plane, from a standard apical four-chamber window. TAPSE was available in a subgroup of 6899 patients. RV function was also evaluated by the peak systolic velocity of the tricuspid annulus by pulsed wave TDI - RV S′ (cm/s).

Evaluation of the variability of TR

To account for the variability of TR distribution patterns, we classified the patients in our cohort in a step by step manner with particular emphasis on particular clinical context.[8] Organic TR was defined at the first step (any congenital or organic cause of TR irrespective of LV function, left valvular function, or pulmonary pressure). After excluding all patients with primary involvement of the valve (either congenital or organic), we were left with all patients with secondary (functional) TR. We then defined patients with functional TR associated with left-sided valvular disease at the second step (TR neither congenital nor organic and occurring in patient with left-sided valve prostheses, repair, any degree of mitral stenosis, or any other native organic valve disease of at least moderate degree) and functional TR associated with left ventricular systolic dysfunction at the third step (TR neither congenital, organic, or left valvular occurring in patients with left ventricular dysfunction with EF < 50%). The remaining patients were then classified as isolated TR (without any of the previously defined causes) if they had systolic pulmonary pressure <50 mmHg, or functional TR associated with pulmonary hypertension if they had systolic pulmonary pressure ≥50 mmHg irrespective of whether it was post-capillary (e.g. diastolic dysfunction), pre-capillary (e.g. pulmonary vascular or parenchymal), or of unspecified cause. After the process of classification, we have entered the classification parameter into the survival models.

Clinical data source and measurement

Age, gender, body mass index, major comorbidities, laboratory values, re-admissions, and all-cause mortality were extracted from the electronic health record. All-cause mortality data are automatically updated in the hospital records from social security via the ministry of health and can be retrieved via identification number.

Statistical methods

Categorical variables were reported as percentages, and continuous variables were reported as mean and standard deviations. Patients were divided into groups according to their TR grade (none/minimal, mild, moderate, or severe). Continuous variables were compared between groups using analysis of variance and categorical variables were compared using the χ^2 test or Fisher's exact test. The Kaplan–Meier curve and log-rank test were used to describe mortality during the follow-up period. Length of follow was described using reverse censoring method. Cox regression was used to evaluate the association between the grade of TR

Table 1 Baseline demographic, clinical, and echo characteristics of hospitalized patients according to TR grade

n = 20 279	None/minimal *n* = 12 345	Mild *n* = 5554	Moderate *n* = 2157	Severe *n* = 223	*P*-value
Baseline demographic and clinical characteristics					
Female	40.3%	51.6%	56.9%	62.8%	<0.001
Age	64.5 (17.2)	75.1 (13.2)	77.9 (12.6)	77.5 (14.3)	<0.001
Lung disease	8.4%	10.4%	11.7%	15.7%	<0.001
Ischaemic heart disease	18.2%	24.9%	29.2%	31.8%	<0.001
Pacemaker/implantable cardioverter defibrillators	1.4%	4.3%	8.0%	12.1%	<0.001
Atrial fibrillation/flutter	7.0%	17.2%	33.6%	49.3%	<0.001
Diabetes mellitus	26.5%	27.7%	28.9%	31.4%	0.028
Obesity	22.2%	18.3%	18.5%	19.3%	<0.001
Hypertension	49.1%	61.5%	65.0%	65.5%	<0.001
Hyperlipidaemia	37.2%	39.7%	39.7%	38.6%	0.006
Renal dysfunction	6.4%	11.2%	14.6%	14.3%	<0.001
Deep vein thrombosis/pulmonary embolism	0.7%	0.8%	1.0%	1.3%	0.293
Malignancy	5.8%	6.8%	6.5%	5.8%	0.089
Cerebrovascular accident/transient ischaemic attack	2.9%	3.1%	3.9%	4.0%	0.047
Length of hospitalization, days (IQR)	6 (3–14)	7 (4–15)	8 (4–16)	9 (5–19)	<0.001
Echocardiographic characteristics					
Mitral stenosis ≥moderate (%)	2.5%	6.3%	10.5%	18.8%	<0.001
Mitral regurgitation ≥moderate (%)	1%	3.3%	6.4%	11.7%	<0.001
Diastolic dysfunction≥ grade 2 (%)	2.5%	6.3%	10.5%	18.8%	<0.001
Aortic stenosis ≥moderate (%)	7.1%	13.1%	15.9%	15.2%	<0.001
Aortic regurgitation ≥moderate (%)	0.4%	0.7%	0.9%	1.8%	<0.001
Tricuspid regurgitation gradient, mmHg, mean (±SD)	16 (3)	19 (5)	23 (7)	34 (11)	<0.001
Systolic pulmonary pressure, mmHg, mean (±SD)	29 (6)	37 (11)	46 (16)	45 (18)	<0.001
Right atrial pressure (mmHg)	6 (3)	7 (5)	11 (6)	17 (3)	<0.001
Right atrial area, cm^2, mean (±SD)	16 (3)	19 (5)	23 (6)	32 (7)	<0.001
Tricuspid annular plane systolic excursion, mm, mean (±SD)	21.7 (4.5)	20.2 (5.2)	17.5 (5.2)	14.8 (4)	<0.001
Right ventricle s′, cm/s, mean ±SD)	12.2 (2.8)	11.4 (3.2)	10 (3.0)	8.7 (2.9)	<0.001
Ejection fraction, %, mean (±SD)	55 (8)	53 (1)	50 (12)	50 (12)	<0.001
Cardiac output, L/min, mean (±SD)	5.3 (1.4)	5.1 (1.5)	4.7 (1.5)	4.1 (1.6)	<0.001
Stroke volume, mL, mean (±SD)	75 (20)	72 (22)	63 (21)	53 (21)	<0.001
Left ventricle mass index, g/m^2, mean (±SD)	98 (28)	115 (31)	125 (32)	207 (73)	<0.001
Left ventricle end-diastolic diameter, mm, mean (±SD)	47 (6)	48 (7)	48 (8)	47 (9)	<0.001
Left ventricle end-systolic diameter, mm, mean (±SD)	30 (7)	31 (9)	32 (10)	32 (11)	<0.001
Left atrial volume index, mL/m^2, mean (±SD)	34 (12)	44 (17)	53 (21)	62 (28)	<0.001
Deceleration time, ms, mean (±SD)	209 (65)	204 (69)	183 (6)	170 (60)	<0.001
E lateral, cm/s, mean (±SD)	8.3 (3.2)	7.5 (2.7)	7.7 (2.6)	8.6 (2.8)	<0.001
E septal, cm/s, mean (±SD)	6.2 (2.3)	5.6 (1.9)	5.5 (1.9)	5.9 (2.1)	<0.001
E/e average, mean (±SD)	10.2 (5.7)	13.0 (7.2)	14.7 (8.2)	13 (6.6)	<0.001
A wave, m/s, mean (±SD)	0.83 (0.31)	0.86 (0.35)	0.76 (0.36)	0.66 (0.34)	<0.001
E wave, m/s, mean (±SD)	0.77 (0.28)	0.91 (0.34)	1.04 (0.42)	1.1 (0.42)	<0.001
E/*A* ratio, mean (±SD)	1 (0.5)	1.2 (0.7)	1.5 (1)	1.8 (1.4)	<0.001

and overall mortality, 1-year mortality, as well as to re-admissions due to heart failure. Univariate Cox regression was used to describe the non-adjusted association between TR grade and long-term outcomes. Multivariate Cox regression was used to study the association after controlling for age and gender, as well as multiple echo parameters [≥moderate aortic stenosis, ≥moderate aortic regurgitation, ≥moderate mitral stenosis, ≥moderate mitral regurgitation, diastolic dysfunction ≥moderate, systolic pulmonary pressure, LV EF, SV, left atrial volume index (LAVI), *E*/e′, and TAPSE] for all patients. Because baseline clinical characteristics (lung disease, ischaemic heart disease, pacemaker/implantable cardiac defibrillator, atrial fibrillation/flutter, diabetes mellitus, obesity, hypertension, hyperlipidaemia, renal dysfunction, deep vein thrombosis/pulmonary embolism, malignancy, and cerebrovascular accident/transient ischaemic attack) were not reported in the majority of ambulatory patients, adjustment for these parameters was performed only for hospitalized patients (analysis was performed separately for

Table 2 Baseline demographic and echo characteristics of all patients according to TR grade

n = 33 305	None/minimal 23 045	Mild 7297	Moderate 2682	Severe 281	*P*-value
Female gender (%)	43.1%	52.8%	56.6%	63.0%	<0.001
Age, mean (±SD)	60.6 (18.2)	73.8 (13.8)	77.2 (12.6)	76.7 (14.6)	<0.001
Mitral stenosis ≥moderate (%)	2.0%	6.6%	11.6%	17.8%	<0.001
Mitral regurgitation ≥moderate (%)	1.0%	3.6%	6.8%	12.1%	<0.001
Diastolic dysfunction≥ grade 2 (%)	2.0%	6.6%	11.6%	17.8%	<0.001
Aortic stenosis ≥moderate (%)	5.8%	13.2%	16.0%	15.7%	<0.001
Aortic regurgitation ≥moderate(%)	0.4%	0.7%	0.9%	1.4%	<0.001
Tricuspid regurgitation gradient, mmHg, mean (±SD)	16 (4)	19 (5)	24 (7)	34 (11)	<0.001
Systolic pulmonary pressure, mmHg, mean (±SD)	29 (5)	36 (11)	46 (16)	46 (18)	<0.001
Right atrial pressure (mmHg)	5 (3)	7 (5)	11 (6)	17 (3)	<0.001
Right atrial area, cm^2, mean (±SD)	16 (3)	19 (5)	23 (6)	32 (7)	<0.001
Tricuspid annular plane systolic excursion, mm, mean (±SD)	22.5 (4.5)	20.7 (5.3)	18 (5.5)	15.5 (4.7)	<0.001
Right ventricle s′, cm/s, mean (±SD)	12.3 (2.7)	11.5 (3.2)	10.2 (3.1)	8.9 (3)	<0.001
RV dilatation (%)	1.1	4.6	15.9	28.5	<0.001
Ejection fraction, %, mean (±SD)	57 (7)	54 (9)	52 (11)	50 (13)	<0.001
Cardiac output, L/min, mean (±SD)	5.3 (1.4)	5.2 (1.5)	4.8 (1.5)	4.1 (1.6)	<0.001
Stroke volume, mL, mean (±SD)	76 (19)	73 (22)	64 (21)	53 (21)	<0.001
Left ventricle mass index, g/m^2, mean (±SD)	96 (29)	119 (36)	133 (36)	207 (73)	<0.001
Left ventricle end-diastolic diameter, mm, mean (±SD)	47 (6)	48 (7)	48 (8)	47 (9)	<0.001
Left ventricle end-systolic diameter, mm, mean (±SD)	29 (6)	31 (8)	32 (10)	33 (11)	<0.001
Left atrial volume index, mL/m^2, mean (±SD)	33 (12)	44 (17)	54 (21)	62 (28)	<0.001
Deceleration time, ms, mean (±SD)	208 (62)	205 (69)	183 (61)	169.45 (58)	<0.001
E lateral, cm/s, mean (±SD)	9.1 (3.6)	7.7 (2.8)	7.8 (2.7)	8.8 (2.9)	<0.001
E septal, cm/s, mean (±SD)	6.8 (2.5)	5.7 (2)	5.6 (1.9)	6 (2.2)	<0.001
E/e average, mean (±SD)	9.5 (5.3)	12.8 (7.2)	14.5 (8)	13.2 (6.7)	<0.001
A wave, m/s, mean (±SD)	0.78 (0.3)	0.86 (0.35)	0.76 (0.35)	0.65 (0.31)	<0.001
E wave, m/s, mean (±SD)	0.77 (0.26)	0.91 (0.34)	1.03 (0.41)	1.12 (0.4)	<0.001
E/*A* ratio, mean (±SD)	1.1 (0.5)	1.2 (0.7)	1.5 (1)	1.8 (1.3)	<0.001

ambulatory and hospitalized patients). Age and gender were forced into the multivariate analysis while other parameters were considered for inclusion in the final model using backward selection method (Wald test was used as criteria, $P > 0.1$ for exclusion). Hazard ratio (HR) and 95% confidence interval (CI) were reported. Multivariate logistic regression was used to evaluate the association between TR and 30-day mortality. Variable selection method was the same as described earlier for the Cox regression. Odds ratio and 95% CI were reported. A two-tailed *P*-value <0.05 was considered as statistically significant. All statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, Version 25.0, IBM Corp, released 2017, Armonk, NY, USA) and R software (version 3.3.3, R Foundation for Statistical Computing, released 2017, Vienna, Austria).

Results

Overall, 33 305 patients were included in the final analysis. Among these patients, in 20 279 (60.9%) echocardiography evaluation was performed during hospitalization while 13 026 (39.1%) were ambulatory patients examined as outpatients. Median age was 65 ± 18 years, and 46.5% were females. In the majority of our cohort (69.2%, *n* = 23 045), there was no or only minimal degree of TR. Mild degree of TR was present in 7297 patients (21.9%), moderate TR was present in 2682 (8%) patients, and 281 (0.8%) had severe TR. Overall prevalence of significant TR was higher in the hospitalized patients than in the ambulatory patients. In hospitalized patients, mild degree of TR was present in 5554 patients (27%), moderate TR was present in 2157 (11%) patients, and 223 (1.1%) had severe TR. In ambulatory patients, mild degree of TR was present in 1743 patients (13%), moderate TR was present in 525 (4%) patients, and 58 (0.45%) had severe TR.

Clinical parameters of the 20 279 hospitalized patients, stratified by severity of TR are shown in *Table 1*. Compared with patients with none or minimal TR, those with at least mild TR were significantly older and had increased prevalence of comorbidities such as ischaemic heart disease, atrial fibrillation, DM, hypertension, lung diseases, and renal dysfunction.

Echocardiographic characteristics

Echocardiographic parameters stratified by TR severity are shown in *Table 1* for hospitalized patients, *Table 2* for all patients, and Supplementary data online, *Table S1* for ambulatory patients.

Table 3 Mortality rates of all patients, and stratified to ambulatory or hospitalized patients according to TR grade compared to none/minimal

Morality	TR	%	Crude HR (95% CI)	*P*-value
All patients				
1-year	None/trace	7.7	1	<0.001
	Mild	16.8	2.29 (2.13–2.47)	<0.001
	Moderate	29.5	4.4 (4.04–4.78)	<0.001
	Severe	45.6	7.64 (6.38–9.14)	<0.001
Overall	None/trace	15.2	1	<0.001
	Mild	32.8	2.39 (2.27–2.52)	<0.001
	Moderate	48.1	4.21 (3.95–4.49)	<0.001
	Severe	61.6	6.36 (5.46–7.41)	<0.001
Hospitalized patients				
1-year	None/trace	12.4	1	
	Mild	20.1	1.7 (1.58–1.84)	<0.001
	Moderate	33.7	3.13 (2.87–3.42)	<0.001
	Severe	51.6	5.44 (4.5–6.58)	<0.001
Overall	None/trace	23.3	1	
	Mild	38.7	1.82 (1.72–1.93)	<0.001
	Moderate	53.1	3.03 (2.83–3.25)	<0.001
	Severe	66.4	4.58 (3.89–5.41)	<0.001
Ambulatory patients				
1-year	None/trace	2.3	1	
	Mild	6.0	2.69 (2.14–3.38)	<0.001
	Moderate	12.4	5.70 (4.34–7.49)	<0.001
	Severe	22.4	11.57 (6.62–20.21)	<0.001
Overall	None/trace	5.9	1	
	Mild	13.8	2.54 (2.19–2.94)	<0.001
	Moderate	27.4	5.70 (4.75–6.83)	<0.001
	Severe	43.1	9.87 (6.62–14.72)	<0.001

Compared with patients with none or minimal TR, those with ≥mild TR had numerous echocardiographic parameters associated with right heart dysfunction: larger RA area, higher estimated RA pressure, and lower TAPSE measurements. In addition, patients with at least mild TR had increased prevalence of systolic and diastolic LV dysfunction, lower stroke volume, and cardiac output, and higher prevalence of additional valvulopathies including mitral stenosis, mitral regurgitation, aortic stenosis, and aortic regurgitation.

Outcome analyses

A total of 7363 (22.1%) patients died during a median follow-up period of 3.34 years [interquartile range (IQR) 2.11–4.54]. One-year mortality rates were 7.7%, 16.8%, 29.5%, and 45.6% for patients with no, mild, moderate, and severe TR respectively ($P < 0.001$; *Table 3*). *Figures 1–3* show the Kaplan–Meier survival curves according to TR severity. Univariable analyses demonstrated increased short (30-day) and mid-term (median follow-up 3.34 years) overall mortality, as well as increased rate of heart failure re-admissions, according to TR severity ($P < 0.001$ for all trends). Multivariable analyses indicated that mortality increased with increasing TR severity, independently of age, gender, and baseline clinical and echocardiographic characteristics. Moreover, the proportional hazards method for overall mortality showed that patients with moderate (HR 1.15, 95% CI 1.02–1.3, $P = 0.024$) and severe TR (HR 1.43, 95% CI 1.08–1.88, $P = 0.011$) had a worse prognosis than those with no or minimal TR (*Table 4* and Supplementary data online, *Table S2*). The overall mortality stratified for TR aetiology according to TR grade is presented in Supplementary data online, *Table S3*. Patients with different TR aetiologies (left-sided valvular, LV dysfunction, functional TR, and isolated TR) had a worse prognosis than those with no or trace TR. Patients with organic TR (any congenital or organic cause of TR irrespective of LV function, left valvular function, or pulmonary pressure) demonstrated a trend towards worse prognosis than those with no or trace TR.

The relationship between severity of TR and heart failure hospitalization is presented in *Figure 4*. Univariable and multivariable analyses indicated that the rate of heart failure hospitalization was also positively correlated with TR severity (*Table 4*).

In a sample of 6899 of the patients (5237 hospitalized patients and 1662 ambulatory patients) with quantitative echocardiographic assessment of right ventricular function by TAPSE, we repeated the multivariable analyses adjusted for the same parameters with the addition of TAPSE. The proportional hazards method for 1-year mortality showed that patients with severe TR (HR 1.89, 95% CI 1.29–2.79, $P = 0.001$) had a worse prognosis than those with no or minimal TR after adjustment for TAPSE (*Table 5* and Supplementary data online, *Table S2*).

Discussion

As there is an inherent challenge to determine the clinical consequences of TR, we have decided to analyse its impact in the largest cohort to date, after adjustment for multiple systemic comorbidities, and echo parameters.

The present study provides pioneering evidence that moderate or greater TR is associated with worse prognosis, independently of age, gender, and other multiple comorbidities and echocardiographic potential confounders. Furthermore, we showed that when TR is assessed with qualitative methods, based on present guidelines, patients with moderate TR have poorer clinical outcomes than those with no or minimal TR, even after adjustment for multiple parameters.

TR is a common echocardiographic finding.[1] Defining the impact of TR on outcome is difficult as it is a clinical entity that may variably be associated with various conditions such as RV dysfunction, intrinsic valve lesions, pulmonary hypertension, left systolic or diastolic ventricular dysfunction, atrial fibrillation, and other comorbidities. Thus, reports suggesting that TR severity affects outcome[2,9] are opposed by others that consider even the most severe tricuspid lesions as benign.[5] In their seminal paper, Nath *et al.*[2] have shown that increase in TR severity was associated with poor survival regardless of LVEF or pulmonary artery pressure. However, the authors did not adjust for systemic comorbidities and numerous important echocardiographic variables such as left atrial volume, diastolic grade, or quantitatively assessed RV dysfunction.

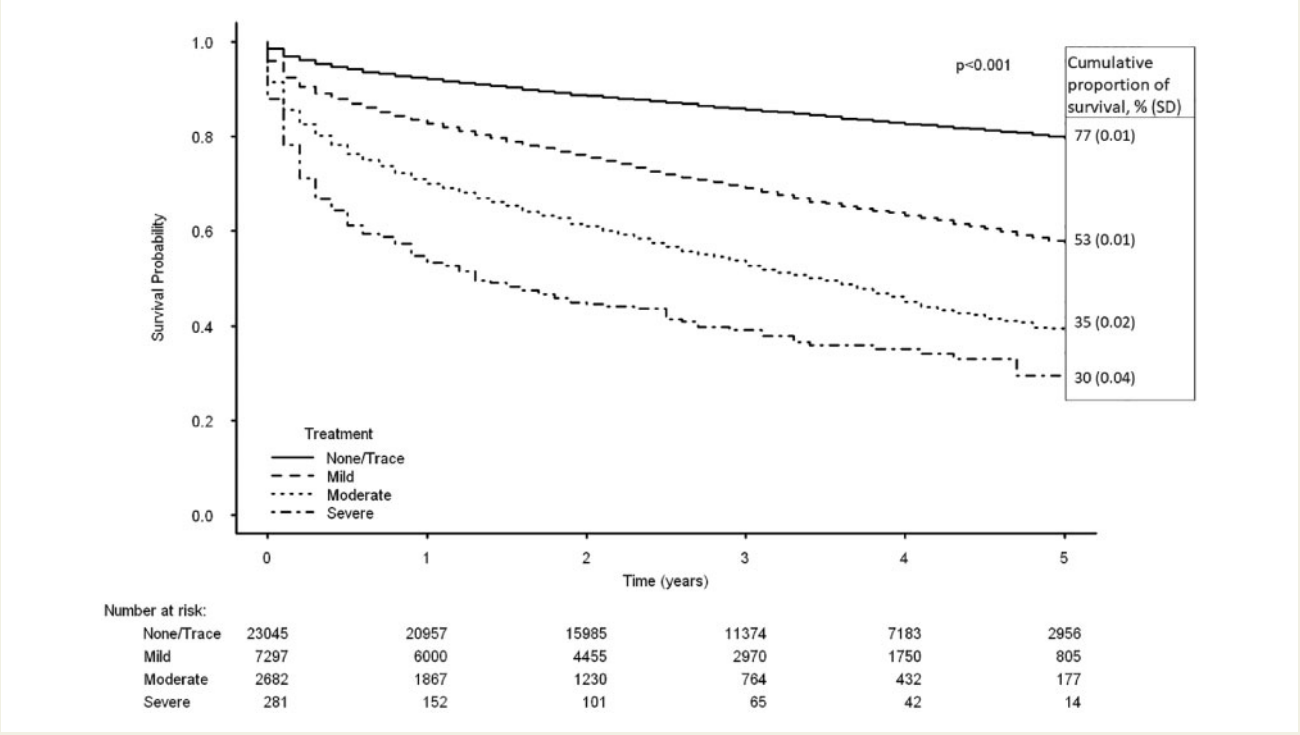

Figure 1 The Kaplan–Meier survival curves of all patients according to TR grade.

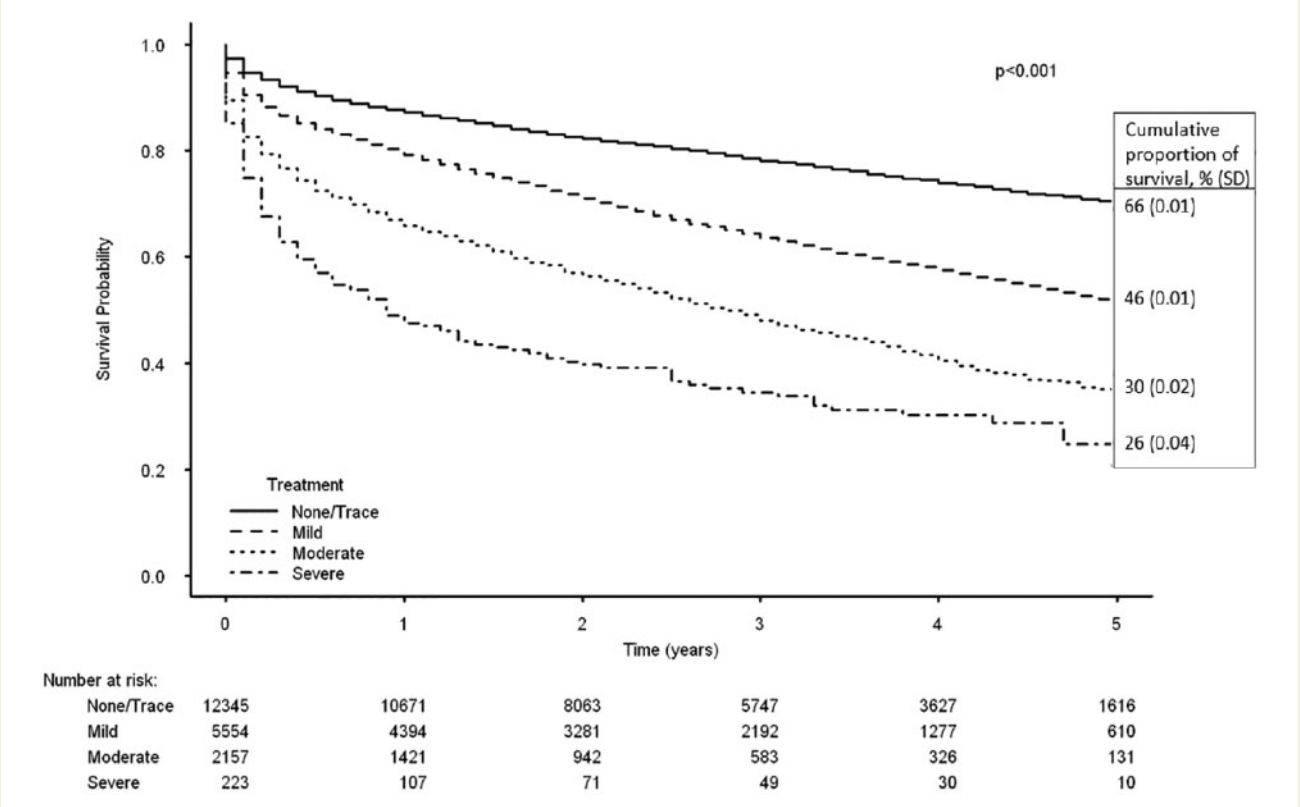

Figure 2 The Kaplan–Meier survival curves of hospitalized patients according to TR grade.

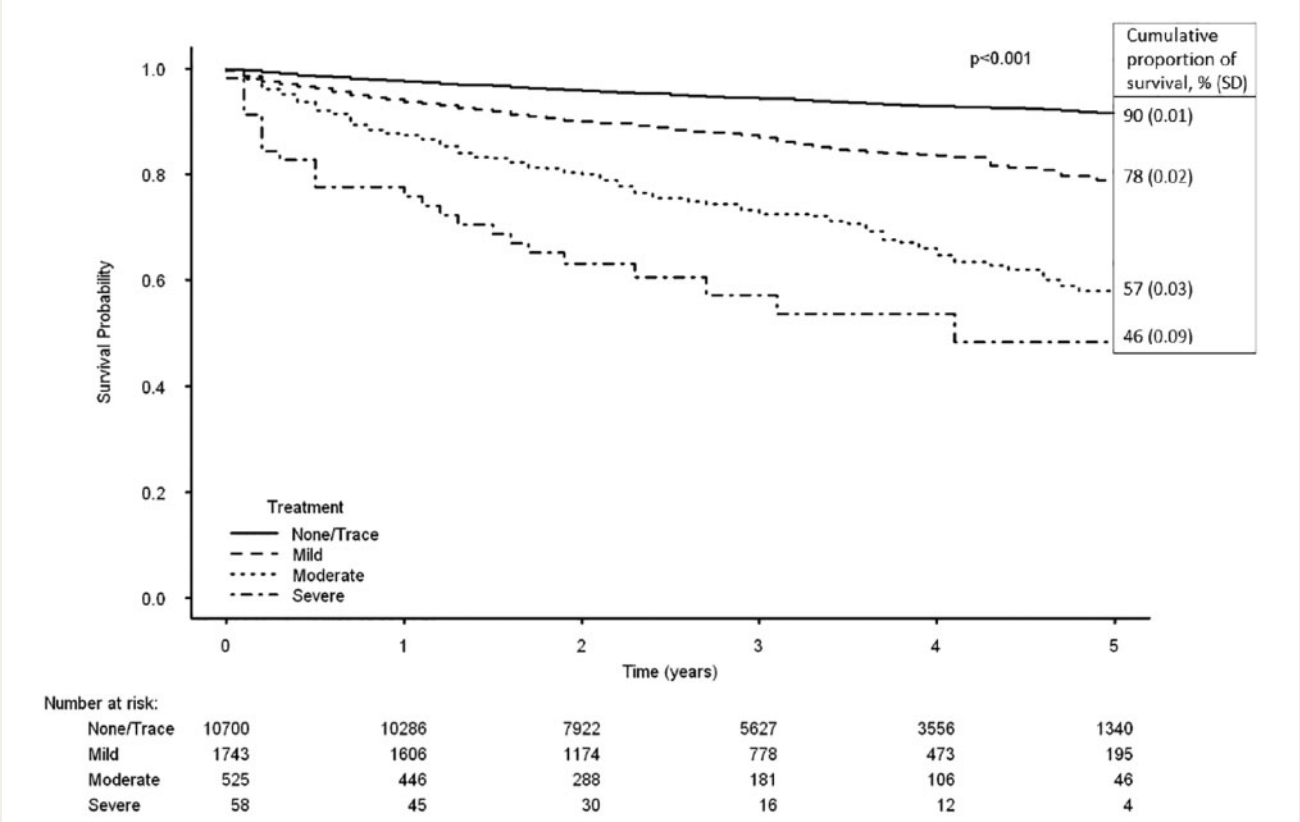

Figure 3 The Kaplan–Meier survival curves of ambulatory patients according to TR grade.

Table 4 Outcomes of hospitalized patients according to TR grade compared to none/minimal

Outcomes	TR	%	Univariate HR (95%CI)	*P*-value	Adj HR[a] (95%CI)	*P*-value	Adj HR[b] (95%CI)	*P*-value
1-year mortality	None/trace	12.4	1		1		1	
	Mild	20.1	1.7 (1.58–1.84)	<0.001	1.23 (1.09–1.37)	<0.001	0.98 (0.87–1.11)	0.775
	Moderate	33.7	3.13 (2.87–3.42)	<0.001	2.15 (1.88–2.45)	<0.001	1.34 (1.14–1.56)	<0.001
	Severe	51.6	5.44 (4.5–6.58)	<0.001	3.46 (2.57–4.66)	<0.001	1.9 (1.39–2.6)	<0.001
Overall mortality	None/trace	23.3	1		1		1	
	Mild	38.7	1.82 (1.72–1.93)	<0.001	1.25 (1.15–1.35)	<0.001	1.01 (0.92–1.1)	0.911
	Moderate	53.1	3.03 (2.83–3.25)	<0.001	1.91 (1.72–2.12)	<0.001	1.15 (1.02–1.3)	0.024
	Severe	66.4	4.58 (3.89–5.41)	<0.001	2.62 (2.02–3.41)	<0.001	1.43 (1.08–1.88)	0.011
Heart failure re-admission	None/trace	2.9	1	1	1		1	
	Mild	6.5	2.29 (1.98–2.65)	<0.001	1.55 (1.26–1.92)	<0.001	1.1 (0.88–1.38)	0.395
	Moderate	10.6	3.94 (3.33–4.65)	<0.001	2.94 (2.31–3.75)	<0.001	1.29 (0.97–1.72)	0.079
	Severe	20.2	7.93 (5.82–10.82)	<0.001	6.81 (4.38–10.57)	<0.001	2.26 (1.38–3.7)	0.001
30-day mortality	None/trace	3.7	1		1		1	
	Mild	7.0	1.98 (1.73–2.28)	<0.001	1.54 (1.22–1.94)	<0.001	1.19 (0.93–1.53)	0.16
	Moderate	13.9	4.23 (3.63–4.93)	<0.001	3.73 (2.89–4.8)	<0.001	2.12 (1.58–2.87)	<0.001
	Severe	18.8	6.08 (4.29–8.61)	<0.001	5.68 (3.26–9.9)	<0.001	2.49 (1.37–4.52)	0.003

[a]Age, gender.
[b]Age, gender, echocardiographic parameters (diastolic dysfunction, left atrium volume index, E/e, stroke volume, systolic pulmonary artery pressure, ejection fraction, aortic insufficiency, aortic stenosis, mitral stenosis, mitral regurgitation), and comorbidities (lung disease, ischaemic heart disease, pacemaker/implantable cardiac defibrillator, atrial fibrillation/flutter, diabetes mellitus, obesity, hypertension, hyperlipidaemia, renal dysfunction, deep vein thrombosis/pulmonary embolism, malignancy, cerebrovascular accident/transient ischaemic attack).

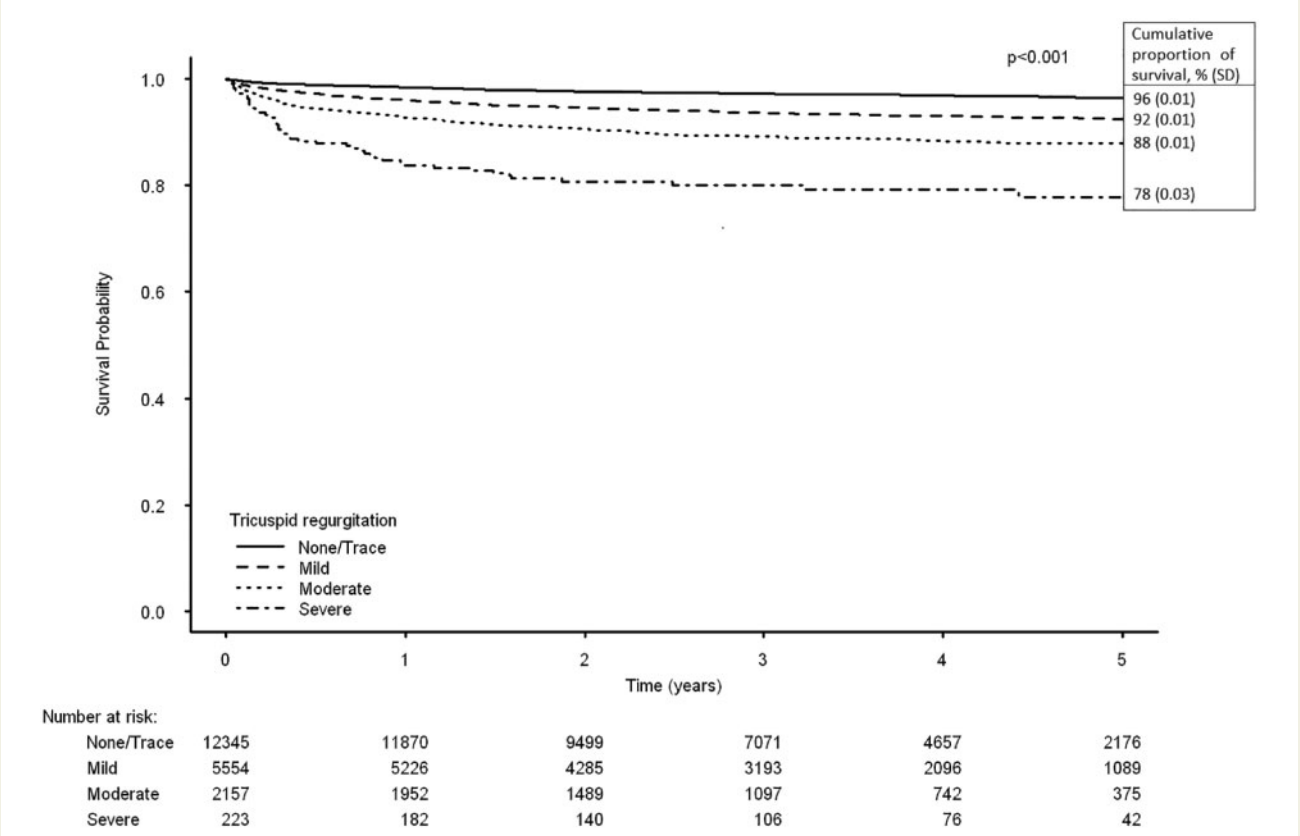

Figure 4 Heart failure re-admissions curves of hospitalized patients according to TR grade.

Table 5 Outcomes of sample of hospitalized patients according to TR grade compared to none/minimal adjusted for TAPSE

Outcomes	TR	%	Crude HR (95% CI)	*P*-value	Adj HR[a] (95% CI) *n* = 5237	*P*-value
1-year mortality	None/trace	12.4	1		1	
	Mild	20.1	1.7 (1.58–1.84)	<0.001	1.02 (0.85–1.23)	0.823
	Moderate	33.7	3.13 (2.87–3.42)	<0.001	1.22 (0.97–1.54)	0.086
	Severe	51.6	5.44 (4.5–6.58)	<0.001	1.89 (1.29–2.79)	0.001
Overall mortality	None/trace	23.3	1		1	
	Mild	38.7	1.82 (1.72–1.93)	<0.001	1 (0.87–1.15)	0.985
	Moderate	53.1	3.03 (2.83–3.25)	<0.001	1.07 (0.89–1.29)	0.447
	Severe	66.4	4.58 (3.89–5.41)	<0.001	1.41 (1.01–1.98)	0.046
Heart failure re-admission	None/trace	2.9	1	1	1	
	Mild	6.5	2.29 (1.98–2.65)	<0.001	1.48 (1.03–2.12)	0.034
	Moderate	10.6	3.94 (3.33–4.65)	<0.001	1.65 (1.08–2.52)	0.021
	Severe	20.2	7.93 (5.82–10.82)	<0.001	3.52 (1.92–6.47)	<0.001
30-day mortality	None/trace	3.7	1		1	
	Mild	7.0	1.98 (1.73–2.28)	<0.001	1.53 (1.04–2.24)	0.032
	Moderate	13.9	4.23 (3.63–4.93)	<0.001	2.61 (1.68–4.05)	<0.001
	Severe	18.8	6.08 (4.29–8.61)	<0.001	3.96 (1.94–8.07)	<0.001

[a]Age, gender, echocardiographic parameters (diastolic dysfunction, left atrium volume index, E/e, stroke volume, systolic pulmonary artery pressure, ejection fraction, aortic insufficiency, aortic stenosis, mitral stenosis, mitral regurgitation, TAPSE), and comorbidities (lung disease, ischaemic heart disease, pacemaker/implantable cardiac defibrillator, atrial fibrillation/flutter, diabetes mellitus, obesity, hypertension, hyperlipidaemia, renal dysfunction, deep vein thrombosis/pulmonary embolism, malignancy, cerebrovascular accident/transient ischaemic attack).

The cause of death in patients with TR remains speculative. Previous reports have suggested that the mechanism of TR related death is progressive RV dysfunction and fibrosis. Progression to clinical complications parallels the pattern of volume overload-related chamber enlargement, leading to increasing TR, and further volume overload.[10,11] Unfortunately the cause of death was not systematically available in our cohort, so the impact of TR on cardiovascular mortality could not be assessed. Thus, we cannot determine the mechanism of increased mortality in TR.

Current guidelines[3,12,13] recommend surgical correction of TR when surgery for left-sided valvular disease is indicated.[14] Until recently, repair or replacement surgery was the only available intervention. However, percutaneous repair procedures for TR are now being avidly studied.[15–18] In view of future availability of these less invasive interventions, it has become vital to analyse the impact of TR on patients' clinical outcomes. We believe that our data may support the rationale of considering the use of minimally invasive percutaneous interventions for the treatment of significant TR, irrespective of the presence of left-sided valve disorders, or left ventricular systolic dysfunction. Nevertheless, large randomized clinical trials should be conducted to affirm the impact of tricuspid interventions on outcomes.

Study limitations

Our study has several limitations. This is a single-centre, observational, retrospective study. Because of its retrospective nature, the study is subject to selection bias, and its results imply association, not cause and effect. Patients with at least moderate to severe TR were older and had numerous additional comorbidities compared with those with less than mild TR. We attempted to control for these differences by using adjusted analysis for systemic and cardiac comorbidities; however, possible effect of these conditions on outcome cannot be excluded. Finally, the causes of death were not available, so the impact of TR on cardiovascular mortality could not be assessed.

Conclusions

In this largest to date study, increase in TR severity was associated with worse prognosis. Considering the strong correlation between TR and mortality presented in this study, we believe our results should serve as an incentive for the conduction of future studies aiming to evaluate the impact of TR interventions on patients' clinical outcomes.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: none declared.

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