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ORIGINAL RESEARCH

# Clinical Outcome of Isolated Tricuspid Regurgitation

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## ABSTRACT

**OBJECTIVES** The aim of this study was to assess the outcome of isolated tricuspid regurgitation (TR) and the added value of quantitative evaluation of its severity.

**BACKGROUND** TR is of uncertain clinical outcome due to confounding comorbidities. Isolated TR (without significant comorbidities, structural valve disease, significant pulmonary artery systolic pressure elevation by Doppler, or overt cardiac cause) is of unknown clinical outcome.

**METHODS** In patients with isolated TR assessed both qualitatively and quantitatively by a proximal isovelocity surface area method, a long-term outcome analysis was conducted. Patients with severe comorbid diseases were excluded.

**RESULTS** The study involved 353 patients with isolated TR (age 70 years; 33% male; ejection fraction, 63%; all with right ventricular systolic pressure <50 mm Hg). Severe isolated TR was diagnosed in 76 patients (21.5%) qualitatively and 68 patients (19.3%) by quantitative criteria (effective regurgitant orifice [ERO] ≥40 $mm^2$). The 10-year survival and cardiac event rates were 63 ± 5% and 29 ± 5%. Severe isolated TR independently predicted higher mortality (adjusted hazard ratio: 1.78 [95% confidence interval (CI): 1.10 to 2.82], $p = 0.02$ for qualitative definition and 2.67 [95% CI: 1.66 to 4.23] for an ERO ≥40 $mm^2$, $p < 0.0001$). The addition of grading by quantitative criteria in nested models eliminated the significance of the qualitative grading and improved the model prediction ($p < 0.001$ for survival and $p = 0.02$ for cardiac events). The 10-year survival rate was lower with an ERO ≥40 $mm^2$ versus <40 $mm^2$ (38 ± 7% vs. 70 ± 6%; $p < 0.0001$), independent of all characteristics, right ventricular size or function, comorbidity, or pulmonary pressure ($p < 0.0001$ for all), and lower than expected in the general population ($p < 0.001$). Freedom from cardiac events was lower with an ERO ≥40 $mm^2$ versus <40 $mm^2$ independently of all characteristics, right ventricular size or function, comorbidity, or pulmonary pressure ($p < 0.0001$ for all). Cardiac surgery for severe isolated TR was rarely performed (16 ± 5% 5 years after diagnosis).

**CONCLUSIONS** Isolated TR can be severe and is associated with excess mortality and morbidity, warranting heightened attention to diagnosis and quantitation. Quantitative assessment of TR, particularly ERO measurement, is a powerful independent predictor of outcome, superior to standard qualitative assessment. (J Am Coll Cardiol Img 2014;7:1185–94)


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**ABBREVIATIONS AND ACRONYMS**

**ERO** = effective regurgitant orifice

**RV** = right ventricular

**SPAP** = systolic pulmonary artery pressure

**TR** = tricuspid regurgitation

Tricuspid regurgitation (TR) is frequent (1) but poorly defined. Management guidelines remain vague (2) due to a paucity of outcome studies and their contradictory results (3–6). Studies of TR are influenced by outcome interference of numerous comorbidities, pulmonary hypertension, left-sided heart disease, and background conditions (4,7,8) that obscure the specific significance of TR (9). Thus, it is generally uncertain whether TR independently affects outcome or is a surrogate for associated conditions. Other sources of uncertainty are the imprecision of standard assessment of TR (10) and the ambiguity of guidelines in defining severe TR (11). Hence, clinical guidelines propose very limited indications for tricuspid valve surgery unless there is another surgical indication such as severe mitral valve diseases (2).

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In trying to resolve this conundrum, we assessed patients with isolated functional TR, excluding major comorbidities affecting TR outcome (9,12–14) and with TR quantitative assessment (11,15,16). We aimed to evaluate clinical outcome of isolated TR, define whether severe isolated TR is associated with excess mortality and cardiac events, and analyze the role of TR quantitative assessment in predicting TR outcome.

## METHODS

**DEFINITION OF ISOLATED TR.** Isolated TR diagnosis required the following: 1) TR holosystolic and functional; 2) no likely pulmonary hypertension (<50 mm Hg) (17); 3) no overt TR cause (no intrinsic tricuspid disease, left ventricular ejection fraction ≥50%, no pacemaker/defibrillator wire across the tricuspid, no other valve disease more than mild, no disease that may cause TR, no congenital or pericardial heart disease); and 4) no previous valve surgery.

**STUDY DESIGN.** We initiated a prospective program of TR quantitation enrolling patients with mild or greater holosystolic TR by visual assessment. The final population was selected retrospectively as patients with isolated TR and TR quantitation performed from 1995 to 2005. Patients with severe comorbid conditions, including cancer, severe lung disease, cirrhosis, recent myocardial infarction (<3 months), or end-stage renal disease at presentation were excluded. Isolated quantified mild to severe TR represented 12.2% of our quantified population. We also identified 1,972 patients with trivial isolated TR (jet area ≤1.0 $cm^2$; an effective regurgitant orifice [ERO] of 0) evaluated by the principal investigator, during the same period, with same inclusion criteria and same methods. To examine the hypothesis that isolated TR of increasing quantified degree is associated with worse outcome consequences, a frequency-matching approach was used in which patients with trivial isolated TR were randomly selected from the desired bin of all patients with trivial isolated TR, achieving groups of patients with trivial and mild to severe quantified TR comparable in terms of other independent determinants of outcome but with no set couples of matched patients and unequal size. The predefined baseline computerized matching parameters were age (within 10 years), ejection fraction (within 5%), exact year of diagnosis, atrial fibrillation, and sex.

Outcome was analyzed from an echocardiographic diagnosis until death or last follow-up up to 2010.

The study was powered (80%, $p = 0.05$) to detect ≥30% mortality difference between severe and lesser degrees of isolated TR. The study was institutional review board approved.

**BASELINE CLINICAL ASSESSMENT AND MANAGEMENT.** Patient symptoms, physical examination, and comorbid conditions (Charlson age-adjusted comorbidity index [18]) were evaluated by Mayo personal physicians. Congestive heart failure was diagnosed by Framingham criteria (19). Clinical management was determined by personal physicians.

**FOLLOW-UP AND OUTCOMES.** Clinical follow-up was obtained by review of medical records, surveys, and telephone interviews. The cause of death was determined by medical records and death certificates. Events used as endpoints were mortality and cardiovascular events under medical management. Cardiovascular events comprised cardiac death including sudden death (20) and congestive heart failure but not death due to other causes.

**DOPPLER ECHOCARDIOGRAPHY.** All measurements were averages of inspiratory and expiratory (21) over ≥5 cardiac cycles (22,23). Right ventricular (RV) size and systolic function were qualitatively graded (on a scale of 1 to 4). RV function assessment was on the basis of multiple views of the right ventricle (short-axis parasternal at basal, mid, and apical levels; lower parasternal RV inflow view; apical 4-chamber view; and, if possible, RV long-axis view and subcostal short- and 4-chamber views). Using these multiple views, integrative qualitative grading was formulated by the physician responsible for the echocardiogram. Qualitative TR assessment used jet size, vena contracta (24), and hepatic venous reversal using recent American Society of Echocardiography

guidelines criteria (11,15,24). TR quantitation used a proximal flow convergence method as validated previously (11,15,16,24). To measure the flow convergence, the color-flow velocity scale was maximized, and the baseline was shifted downward until the flow convergence region was clearly visualized. All possible views were used to obtain the best alignment of flow center line with the beam of ultrasound. We then recorded cines of flow convergence imaging in zoomed views and measured on these loops multiple flow convergence radii, in inspiration and expiration, timed to peak TR velocity (generally on the T-wave of the electrocardiogram). Corrections for the angle of leaflets and for the ratio of aliasing velocity to peak TR velocity (peak velocity)/(peak velocity − aliasing velocity) were applied (21), allowing calculation of regurgitant flow. The ERO area was calculated as the ratio of regurgitant flow to the peak velocity of the TR jet and the regurgitant volume as the product of the ERO × the regurgitant time-velocity integral.

**STATISTICAL ANALYSIS.** Descriptive results were expressed as mean ± SD (continuous variables) and percents (categorical variables). Group comparisons used analysis of variance, Fisher exact, or the chi-square test, as appropriate. Multiple comparisons for continuous and categorical parameters used Tukey-Kramer honestly significant difference test and Bonferroni correction, respectively. Analysis of association of severe TR with outcome was based primarily on quantitative TR definition (ERO ≥40 $mm^2$), but standard qualitative classification was also used and incremental value tested by nested models with F tests. Endpoints were death of any cause and cardiac events under medical management (from diagnosis to surgery or death), and data were censored at the time of cardiac surgery if it was performed or at the time of noncardiac death. Event rates were estimated by the Kaplan-Meier method and compared by the log-rank test. Comparison of observed to expected mortality used U.S. Census-Bureau life tables and the log-rank test. Cox proportional hazards models calculated hazard ratios associated with severe TR, unadjusted and adjusted for age, sex, ejection fraction, pulmonary pressure, RV size, RV function, and atrial fibrillation, which were selected a priori and hierarchical on the basis of their biological impact on survival. Values of $p < 0.05$ were considered significant.

## RESULTS

**BASELINE CHARACTERISTICS.** Table 1 shows baseline characteristics of the 353 patients, overall and stratified as patients with quantified isolated TR (mild to severe quantified TR) versus patients with trivial TR. Age, sex, ejection fraction, systolic blood pressure, hemoglobin, bilirubin, age/comorbidity index, and atrial fibrillation were equally distributed. Dyspnea, chest pain, and ankle swelling were more frequent in patients with more than trivial isolated TR (all p values <0.001). However, there was no difference in symptoms between trivial and mild to moderate (ERO, 1 to 39 $mm^2$) TR.

**TABLE 1 Baseline Characteristics of Patients With Functional TR Overall and Stratified by Severity of Regurgitation**

| | All Isolated Functional TR (N = 353) | Trivial Isolated Functional TR (n = 211) | Mild to Severe Isolated Functional TR (n = 142) | p Value |
|---|---|---|---|---|
| Age, yrs | 70 ± 14 | 70 ± 14 | 71 ± 14 | 0.26 |
| Atrial fibrillation | 157 (44) | 95 (45) | 62 (44) | 0.80 |
| Male | 115 (33) | 71 (34) | 44 (31) | 0.60 |
| Systolic blood pressure, mm Hg | 129 ± 20 | 130 ± 19 | 128 ± 20 | 0.36 |
| Hemoglobin, g/l | 13.3 ± 1.6 | 13.4 ± 1.7 | 13.1 ± 1.6 | 0.07 |
| Creatinine, mg/dl | 1.13 ± 0.5 | 1.12 ± 0.3 | 1.14 ± 0.7 | 0.68 |
| Bilirubin, mg/dl | 0.71 ± 0.4 | 0.75 ± 0.5 | 0.68 ± 0.3 | 0.20 |
| Ejection fraction, % | 63 ± 6 | 64 ± 6 | 63 ± 6 | 0.12 |
| Age/comorbidity index | 4.7 ± 3.0 | 4.7 ± 2.8 | 4.7 ± 3.2 | 0.80 |

Values are mean ± SD or n (%).
TR = tricuspid regurgitation.

Clinical and echocardiographic assessments classified by quantitative grades of TR are presented in Table 2. The prevalence of murmur increased with severe regurgitation but rarely with inspiratory variation. Heart failure was more prevalent in severe TR despite greater use of diuretic agents (41% vs. 16% and 13% in mild to moderate and trivial TR, $p < 0.0001$). Similar to mitral regurgitation (25) in isolated TR, enlarged RV end-diastolic and end-systolic areas with worsening TR reflect altered end-systolic characteristics but allow increased regurgitant volume, whereas cardiac index decreases little and RV area contraction displays nonsignificant changes. Hemodynamic assessment showed significant but slight systolic pulmonary pressure differences with averages well within unlikely pulmonary hypertension and in all patients below thresholds defining likely pulmonary hypertension (17).

**SURVIVAL AFTER DIAGNOSIS.** There were 82 deaths under medical management during follow-up (5.8 ± 3.2 years). Quantified TR degree was strongly associated with decreased survival (Table 3). However, the ERO was a more powerful predictor of survival than regurgitant volume ($p < 0.01$) so that all subsequent analyses focused on the ERO.

**TABLE 2 Objective Tricuspid-Related Clinical and Echocardiographic Characteristics**

| | Isolated Tricuspid Regurgitation Severity | | | |
|---|---|---|---|---|
| | Trivial (n = 211) | Mild-Moderate (n = 74) | Severe (n = 68) | p Value |
| Clinical characteristics | | | | |
| Systolic murmur, % | 27 | 35 | 68*† | <0.0001 |
| Inspiratory increase of murmur, % | 0.5 | 4.0 | 15*† | <0.0001 |
| Increased jugular venous pressure, % | 2 | 14* | 38*† | <0.0001 |
| Hepatojugular reflux, % | 0.5 | 4 | 19*† | <0.0001 |
| Edema, % | 13 | 12 | 49*† | <0.0001 |
| Heart rate, beats/min | 75.4 ± 17.4 | 71.3 ± 17.2 | 72.0 ± 17.8 | 0.14 |
| Doppler echocardiography characteristics | | | | |
| Effective regurgitant orifice, $mm^2$ | 0 | 27 ± 8* | 68 ± 37*† | <0.0001‡ |
| Regurgitant volume, ml/beat | 0 | 23.7 ± 7.9* | 51.4 ± 18.0*† | <0.0001‡ |
| Jet area, $cm^2$ | <1 | 6.6 ± 3.5* | 10.4 ± 4.9*† | <0.0001‡ |
| Vena contracta, mm | <2 | 4.8 ± 1.6* | 6.7 ± 2.6*† | <0.0001‡ |
| Tricuspid regurgitant peak velocity, m/s | 2.5 ± 0.3 | 2.7 ± 0.3* | 2.6 ± 0.3* | <0.0001 |
| Estimated right atrial pressure, mm Hg | 6.0 ± 2.1 | 8.9 ± 4.0* | 11.9 ± 5.6*† | <0.0001 |
| Right ventricular systolic pressure, mm Hg | 30.7 ± 6.0 | 39.3 ± 6.9* | 40.0 ± 6.8* | <0.0001 |
| Cardiac index, l/min/$m^2$ | 2.9 ± 0.7 | 2.8 ± 0.7 | 2.6 ± 0.5* | 0.002 |
| E/A ratio | 1.04 ± 0.5 | 1.06 ± 0.5 | 1.1 ± 0.5 | 0.9 |
| E/e′ | 11.8 ± 0.3 | 11.7 ± 4.3 | 11.6 ± 4.1 | 0.9 |
| Diastolic grade, % | 0, 11; I, 37; II, 52 | 0, 16; I, 38; II, 45 | 0, 10; I, 27; II, 62 | 0.3 |
| RV enlargement moderate or severe, % | 2 | 19* | 40*† | <0.0001 |
| RV end-diastolic area indexed, $cm^2/m^2$ | 11.9 ± 2.5 | 13.9 ± 3.3 | 17.0 ± 0.5*† | <0.0001 |
| RV end-systolic area indexed, $cm^2/m^2$ | 6.7 ± 2.0 | 8.6 ± 2.3 | 10.8 ± 4.1*† | <0.0001 |
| RV function reduction moderate or severe, % | 0 | 4 | 4.5§ | 0.004 |
| RV fractional area change, % | 44.5 ± 8.0 | 38.0 ± 11.0 | 37.2 ± 11.0 | 0.2 |
| RIMP | 0.32 ± 0.08 | 0.42 ± 0.18 | 0.44 ± 0.2 | 0.3 |

Values are mean ± SD. Mild-moderate and severe tricuspid regurgitation are defined on the basis of effective regurgitant orifice 1 to 39 $mm^2$ and ≥40 $mm^2$ respectively. *p < 0.001 versus trivial TR. †p < 0.001 versus mild-moderate isolated TR. ‡p < 0.05. §p < 0.05.

E/A = ratio of mitral inflow peak early diastolic flow-velocity to atrial contraction peak-velocity; E/e′ = ratio of mitral inflow peak early diastolic flow-velocity to septal mitral-annulus tissue Doppler early diastolic-velocity; RIMP = right ventricular index of myocardial performance RV = right ventricular.

Clinical characteristics predictive of higher mortality were older age (adjusted hazard ratio [HR]: 1.09 [95% confidence interval (CI): 1.06 to 1.12] per year; p < 0.001), lower systolic-blood-pressure (adjusted HR: 0.98 [95% CI: 0.99 to 0.97] per mm Hg; p = 0.02), symptoms (adjusted HR: 2.0 [95% CI: 1.3 to 3.0]; p < 0.01), and atrial fibrillation at diagnosis (adjusted HR: 1.77 [95% CI: 1.14 to 2.79], p = 0.01). Echocardiographic characteristics predictive of higher mortality are shown in Table 3. Addition of the ERO to models showed severe TR (≥40 $mm^2$) independently associated with lower survival (Table 4) with improved model predictive power (p < 0.001).

**TABLE 3 Impact of Clinical and Echocardiographic Characteristics on Mortality in Patients With Idiopathic Isolated Tricuspid Regurgitation**

| | HR (95% CI) | p Value |
|---|---|---|
| Effective regurgitant orifice, $cm^2$ | 3.50 (2.20–5.20) | <0.0001 |
| Regurgitant volume, ml/beat | 1.02 (1.01–1.03) | <0.0001 |
| Tricuspid regurgitant peak velocity, m/s | 1.03 (0.99–1.06) | 0.08 |
| Estimated right atrial pressure, mm Hg | 1.07 (1.02–1.12) | 0.003 |
| Right ventricular systolic pressure, mm Hg | 1.04 (1.02–1.07) | 0.001 |
| Cardiac index, l/min/$m^2$ | 0.83 (0.60–1.13) | 0.2 |
| E/A ratio | 1.00 (0.40–2.06) | 0.9 |
| E/e′ | 1.06 (1.00–1.11) | 0.05 |
| Diastolic grade | – | 0.02 |
| RV size (visual estimation) | – | 0.01 |
| RV end-diastolic area indexed, $cm^2/m^2$ | 1.10 (1.03–1.17) | 0.002 |
| RV end-systolic area indexed, $cm^2/m^2$ | 1.14 (1.04–1.23) | 0.007 |
| RV function (visual estimation) | – | 0.03 |
| RV fractional area change, % | 3.90 (0.25–6.20) | 0.3 |
| RIMP | 1.03 (0.20–5.20) | 0.9 |

CI = confidence interval; HR = hazard ratio; RIMP = right ventricular index of myocardial performance; RV = right ventricular; other abbreviations as in Table 2.

Mild to moderate isolated TR showed no difference in survival after diagnosis versus trivial regurgitation, univariably (86 ± 3% vs. 90 ± 4% at 5 years, p = 0.23) or in multivariable models (p = 0.34). Subdivision of the mild to moderate range into mild (1 to 19 $mm^2$) and moderate (20 to 39 $mm^2$) did not yield survival differences (p = 0.42). Kaplan-Meier survival curves (Figure 1) show considerable survival difference between severe and lesser degrees of isolated TR (ERO ≥40 $mm^2$ vs. <40 $mm^2$).

Overall, observed versus expected survival was not different (63% vs. 62% expected at 10 years, p = 0.80).

**TABLE 4 Impact of Severe Regurgitation (Effective Regurgitant Orifice ≥40 $mm^2$) on Mortality and Cardiovascular Events Risk After the Diagnosis of Idiopathic Isolated Tricuspid Regurgitation**

| | HR | 95% CI | p Value |
|---|---|---|---|
| Mortality after diagnosis | | | |
| Univariable analysis | 3.34 | 2.12–5.20 | <0.001 |
| Adjusted* | 2.67 | 1.66–4.23 | <0.001 |
| Comprehensive adjustment† | 2.95 | 1.67–5.19 | <0.001 |
| Cardiac events | | | |
| Univariable analysis | 6.62 | 3.87–11.46 | <0.001 |
| Adjusted‡ | 3.98 | 2.15–7.45 | <0.001 |
| Comprehensive adjustment† | 4.77 | 2.40–9.60 | <0.001 |

*Adjustment was for age, systolic blood pressure, and the presence of atrial fibrillation. †Adjustment was for age, sex, systolic blood pressure, history of coronary disease, symptoms at diagnosis, Charlson comorbidity index, left ventricular ejection fraction, right ventricular size, right ventricular function, and right ventricular systolic pressure. ‡Adjustment was for age, systolic blood pressure, symptoms, right ventricular systolic pressure, and the presence of atrial fibrillation.

Abbreviations as in Table 3.

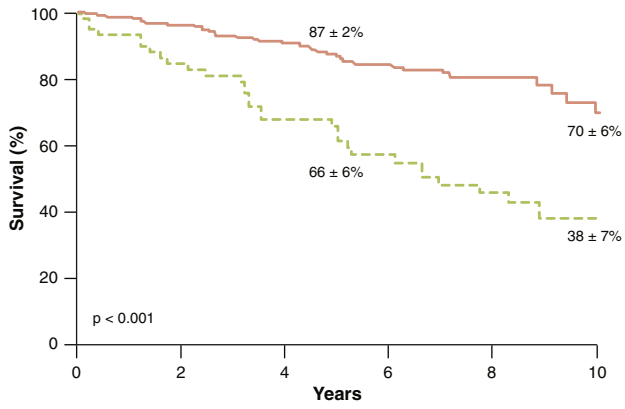
The only group with observed less than expected survival was that with an ERO ≥40 mm² (38% vs. 58% expected at 10 years, p < 0.001).

**CARDIAC EVENTS AFTER DIAGNOSIS.** During follow-up under conservative management, 55 patients experienced cardiac events, 20 heart failure, and 45 cardiac death or both. The ERO of TR was strongly associated with higher event rates (Table 4).

Background clinical and echocardiographic characteristics predictive of higher event rates were older age (adjusted HR: 1.08 [95% CI: 1.05 to 1.12] per year; p < 0.001), lower systolic blood pressure (adjusted HR: 0.98 [95% CI: 0.97 to 0.99] per mm Hg; p = 0.02), symptoms (adjusted HR: 3.3 [95% CI: 1.9 to 5.6]; p < 0.001), atrial fibrillation at diagnosis (adjusted HR: 2.8 [95% CI: 1.6 to 4.7]; p < 0.01) and RV systolic-pressure (adjusted HR: 1.09 [95% CI: 1.05 to 1.13] per mm Hg; p < 0.01). Addition of the ERO to models showed severe TR (≥40 mm²) independently associated with higher event rates (Table 4) and increased model predictive power (p < 0.001). Mild to moderate versus trivial isolated TR showed no differences in cardiac events univariably (6 ± 3% vs. 6 ± 2% at 5 years, p = 0.33) or multivariably (p = 0.16). Subdivision of mild to moderate range into mild and moderate showed no difference in events (p = 0.39). Kaplan-Meier curves (Figure 2) show considerably higher cardiac event rates after diagnosis in severe versus lesser isolated TR. Severe TR (ERO >0.4 cm²) was associated with an increased rate of sudden death (hazard ratio: 3.5 [95% CI: 1.6 to 7.6]; p = 0.003). The 5-year rate of sudden death was 3.0 ± 1.0% versus 14.5 ± 4.0%; p = 0.008 for patients with an ERO <0.4 cm² and an ERO >0.4 cm², respectively.

**SUBGROUP ANALYSIS.** Outcomes in sinus rhythm and atrial fibrillation are shown Figure 3, demonstrating similarly lower survival and higher cardiac event rates with severe isolated TR irrespective of rhythm at baseline. Multivariable analysis stratified by baseline rhythm shows that severe isolated TR independently determines lower survival in sinus rhythm (adjusted HR: 2.2 [95% CI: 1.02 to 5.7]; p = 0.01) and atrial fibrillation (adjusted HR: 3.7 [95% CI: 1.4 to 11.7]; p = 0.004) with higher cardiac event rates in sinus rhythm (adjusted HR: 3.5 [95% CI: 1.4 to 8.8]; p = 0.002) and atrial fibrillation (adjusted HR: 3.3 [95% CI: 1.3 to 10.1]; p = 0.001).

Patients were also stratified by symptom status as asymptomatic (65%) or symptomatic (35%). Survival and cardiac event rates were worse in patients with symptoms at baseline. The 5-year survival rate was 84.7 ± 2.5% versus 77.6 ± 3.9% in asymptomatic versus symptomatic isolated TR (p = 0.001), and freedom from cardiac events was 93.3 ± 1.8%



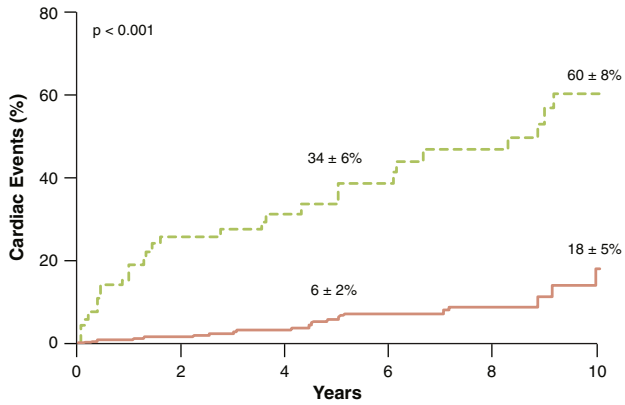

**Number at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Total** | 353 | 308 | 252 | 194 | 70 | 31 |
| **ERO <40** | 285 | 253 | 210 | 163 | 46 | 23 |
| **ERO ≥40** | 68 | 55 | 42 | 31 | 24 | 8 |

ERO ≥40 mm² — ERO <40 mm²

**FIGURE 1 Survival in Patients With Isolated TR, Stratified According to ERO**

Overall survival in patients with isolated tricuspid regurgitation (TR) stratified according to the effective regurgitant orifice (ERO). Severe with ERO ≥40 mm² **(dashed line)** versus trivial to moderate with ERO <40 mm² **(solid line)**. The values indicated for each line are survival rates (±SE) at 5 and 10 years.




**Number at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Total** | 353 | 294 | 242 | 183 | 65 | 29 |
| **ERO <40** | 285 | 252 | 209 | 160 | 46 | 23 |
| **ERO ≥40** | 68 | 42 | 33 | 23 | 19 | 6 |

ERO ≥40 mm² — ERO <40 mm²

**FIGURE 2 Cardiac Events (Cardiac Death or Congestive Heart Failure) in Patients With Isolated TR, Stratified According to the ERO**

The values indicated for each line are cardiac event rates (± SE) at 5 and 10 years. Note that there is no difference in cardiac event rates between patients with trivial, mild, and moderate isolated TR (p = 0.58), but that severe TR is associated with markedly increased cardiac event rates. Abbreviations as in Figure 1.

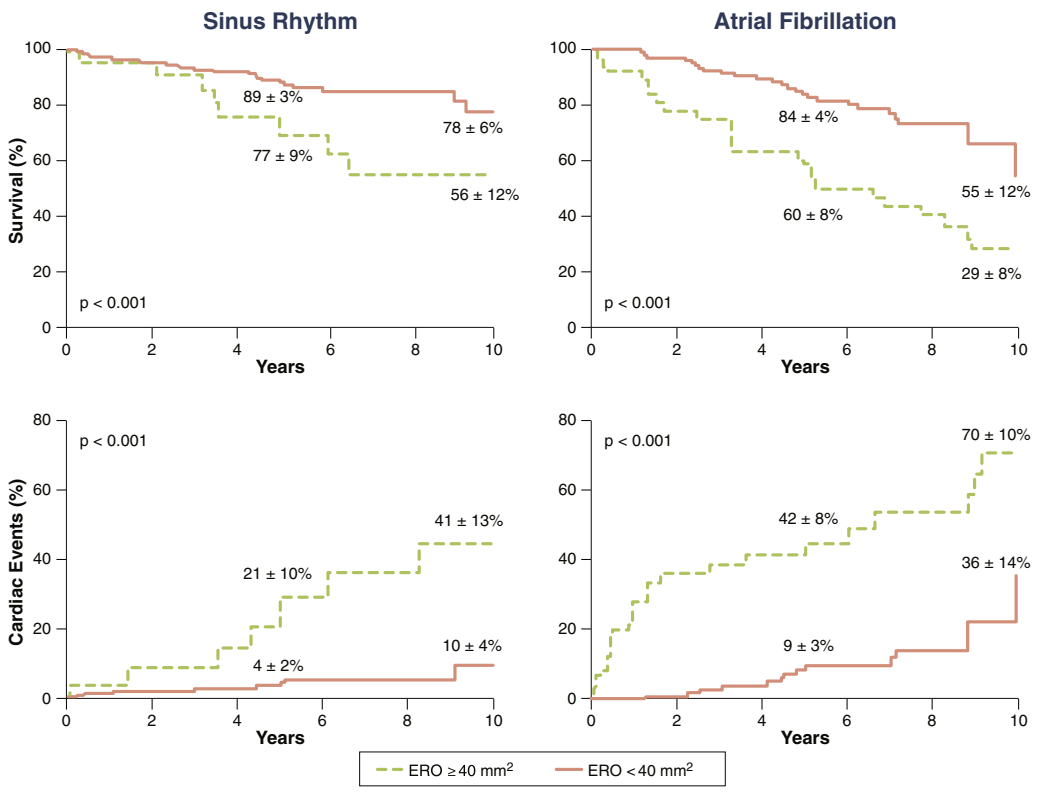



**FIGURE 3 Survival and Cardiac Events in Patients With Isolated TR, Stratified According to ERO and Baseline Rhythm**

Outcome of patients with isolated TR, stratified by atrial rhythm at diagnosis (sinus rhythm, **[left]** and atrial fibrillation **[right]**) comparing those with severe versus trivial to moderate TR defined by the ERO. The graphs in the **top row** indicate overall survival, and those in the **bottom row** indicate cardiac events. Note that there is trend toward more deaths and cardiac events in atrial fibrillation. However, in both atrial fibrillation and sinus rhythm, severe TR is associated with markedly decreased survival and markedly increased cardiac events. Abbreviations as in Figure 1.

versus 80.5 ± 3.9% in asymptomatic versus symptomatic patients ($p < 0.0001$). Outcomes in symptomatic and asymptomatic patients (Figure 4) show lower survival and higher cardiac event rates with severe isolated TR (≥40 $mm^2$ vs. <40 $mm^2$) in both symptom strata, confirmed on multivariable analysis for survival (both $p < 0.01$) and cardiac events (both $p < 0.001$).

We followed the most recent guidelines (17) specifying that pulmonary hypertension is "likely" with a systolic pulmonary artery pressure (SPAP) >50 mm Hg so that such patients were carefully excluded; 219 patients fulfilled criteria for "unlikely pulmonary hypertension" (SPAP ≤36 mm Hg), and 134 were "possible pulmonary hypertension" of 37 to 49 mm Hg. Comparing the "unlikely" and "possible" groups, the 5-year survival rate was similar without severe TR (ERO <0.4 $cm^2$), 86 ± 3% versus 88 ± 3% ($p = 0.6$) and with severe TR (ERO >0.4 $cm^2$), 54 ± 13% versus 61 ± 7% ($p = 0.5$). Multivariable analysis showed that SPAP among our patients did not independently determine mortality ($p = 0.08$) or cardiac events ($p = 0.09$). Stratified by SPAP, severe isolated TR (ERO >0.4 $cm^2$) is associated with a lower survival rate with SPAP <36 mm Hg (5-year 54% vs. 86%, $p < 0.001$) or >36 mm Hg (5-year 61% vs. 88%, $p < 0.001$). Similarly, severe isolated TR is associated with higher cardiac event rates with SPAP <36 mm Hg (5-year 33% vs. 5%, $p < 0.001$) or >36 mm Hg (5-year 31% vs. 5%, $p < 0.001$). Cox proportional hazard analysis with interaction terms for ERO (<0.4 $cm^2$ or ≥0.4 $cm^2$) and SPAP (<36 mm Hg or ≥36 mm Hg) showed that SPAP level does not affect severe isolated TR impact on survival ($p = 0.4$) or cardiac events ($p = 0.33$). On Cox proportional analysis limited to patients with SPAP ≤36 mm Hg, severe TR is highly significantly associated with survival ($p < 0.001$) and cardiac events ($p < 0.001$) on unadjusted analysis and adjusted analysis ($p = 0.005$ for survival and $p = 0.02$ for cardiac events).

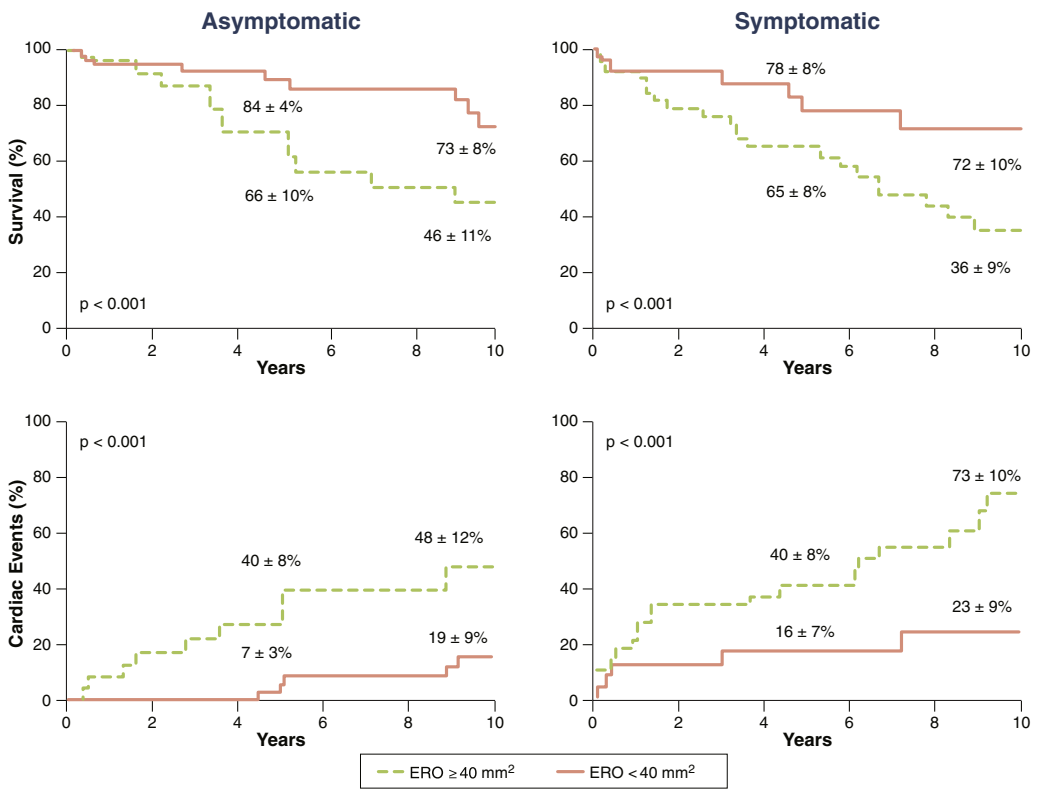



**FIGURE 4** **Survival and Cardiac Events in Patients With Isolated TR, Stratified According to ERO and Baseline Symptoms**

Outcomes of patients with isolated TR, stratified by symptoms at diagnosis (asymptomatic **[left]** and symptomatic **[right]**) comparing those with severe versus trivial to moderate TR defined by the ERO. The graphs in the **top row** indicate overall survival after diagnosis, and the graphs in the **bottom row** indicate cardiac events after diagnosis. The p values were ≤0.001 for all comparisons. Abbreviations as in Figure 2.

**QUANTITATIVE VERSUS QUALITATIVE GRADING OF SEVERE ISOLATED TR.** There were 76 patients graded severe TR qualitatively, and agreement with quantitative grading was significant but suboptimal (kappa = 0.65, $p < 0.01$). Severe TR by qualitative criteria was associated with a lower survival rate (45 ± 8% vs. 69 ± 6% at 10 years, $p < 0.001$), confirmed on multivariable analysis (adjusted HR: 1.78 [95% CI: 1.10 to 2.82], $p = 0.02$) and with higher event rates (57 ± 8% vs. 18 ± 5% at 10 years, $p < 0.001$) confirmed on multivariable analysis (adjusted HR: 3.84 [95% CI: 2.13 to 7.00], $p < 0.001$). However, for both endpoints, addition of severe grading by quantitative criteria in nested models eliminated qualitative grading significance and improved model prediction ($p < 0.001$ for survival and $p = 0.02$ for cardiac events).

**CLINICAL MANAGEMENT AND SURGERY.** Clinical management after diagnosis was medical in 341 patients (97%) and by tricuspid surgery (mean 0.9 ± 1.7 years later) in 12 patients. Surgical indication was on the basis of severe right heart failure symptoms in 7 patients, marked RV dilation in 2 patients, or other indication for cardiac surgery in 3 patients. TR was severe at surgery in all patients who were operated on, and valve repair was performed in 8 (66%) with replacement in the other 4 patients.

## DISCUSSION

Our study, the first to link quantified TR and clinical outcome, shows that the outcome of isolated severe functional TR, independently of other cardiovascular or comorbid conditions, is characterized by excess mortality and excess cardiac events. This independent negative outcome is obvious with any group stratification: symptoms, rhythm, or SPAP. Conversely, no adverse consequence could be detected regarding moderate isolated TR, further emphasizing the importance of precise TR assessment. TR

quantitative assessment, particularly ERO measurement, is the most powerful predictor of outcome, superior to standard qualitative assessment. However, this comparative issue should not overshadow the most important goal of detecting severe TR by any means possible and should raise awareness of its dire consequences.

**TR HETEROGENEITY AND OUTCOME UNCERTAINTY.** Assessing the clinical impact of TR is difficult because it is heterogeneous (26), variably associated with intrinsic valve lesions (27), pulmonary hypertension, ventricular dysfunction, and comorbid or causal diseases (9) that have confused previous attempts to define the TR-specific impact on outcome (3,5,6). The largest outcome study to date suggested that TR of any type may affect outcome (6), but a TR dire outcome could just reflect associated conditions. This uncertainty is further complicated by the imprecision of qualitative grading of TR (10,11,28).

To fill these gaps in knowledge, we designed this study with careful patient selection to minimize heterogeneity of TR etiology and mechanism and to minimize the impact of comorbid conditions (9,12–14).

This process yields robust evidence that severe isolated TR implies excess subsequent mortality and cardiac events. Importantly, using multiple methods, the conceptual heterogeneity in pulmonary hypertension (unlikely vs. possible) did not affect our results, specifically, severe isolated TR affects subsequent outcome irrespective of the included SPAP range, which does not bias the TR role. Our data raise the question of whether severe TR of any cause or mechanism may have similar dire consequences independently of the comorbid or causal disease involved (6), but strict relevance is to isolated TR, which deserves particular attention.

**ASSESSMENT OF TR.** TR is often clinically unsuspected (4,26) and cardiac auscultation is rarely typical. Thus, in routine practice, diagnosis mostly depends on Doppler echocardiography (29). For this purpose, we prefer quantitative grading of TR. The threshold of an ERO of 40 $mm^2$ was suggested by physiological studies (16), but the present data are the first to link this threshold to outcome, survival, and cardiac events, and its prognostic power supersedes that of classic semiquantitative grading (11). However, although weaker, qualitative definition of severe TR also predicted outcome and is important in alerting to the condition and to the need for quantitative assessment (11). Importantly, TR severity may vary due to RV plasticity and varying load. RV widening and annular enlargement decrease systolic annular coverage by leaflets, increasing TR. Hence, persistence of severe functional TR despite treatment is important in therapeutic decisions (30), as less severe TR is associated with preserved outcome, emphasizing the significance of precise TR assessment.

**ETIOLOGY OF ISOLATED TR.** The etiology of isolated TR is not well characterized because exceptional referrals to surgery prevent direct pathological observation (27). Isolated TR was mentioned in several reports (12–14), which described an appearance that is quite different from that of functional TR caused by pulmonary hypertension (9,31) and that of associated right ventricular remodeling, which are fundamentally different (31). With pulmonary hypertension, the right ventricle becomes globular, leading to tethering of tricuspid leaflets (32), similar to functional mitral regurgitation (33). Conversely, isolated TR is characterized by dilation of the RV base and tricuspid annulus, leading to less tethering but exhaustion of the reserve of valvular coverage of the annulus (14,31,34). The exact pathological mechanism of annular enlargement is undefined and may be a degenerative alteration of tricuspid annular fibrous structure (35). Importantly, we show that, irrespective of mechanistic issues and despite a benign façade (17), isolated TR may be severe and may seriously affect outcome.

**CLINICAL IMPLICATIONS.** Although seminal reports suggested that untreated TR is an important contributor to poor outcome (3,5,6,16), the present study provides evidence for the first time that severe isolated TR, irrespective of SPAP level, is associated with excess mortality and cardiac events when it is severe. Furthermore, we show that measurement of ERO using quantitative Doppler echocardiography methods provides the most powerful tools for stratification and management. The ERO threshold of 40 $mm^2$ is linked to clinical outcome, survival, and cardiac events. No adverse consequence could be detected regarding moderate TR ($<$40 $mm^2$) in the specific context of isolated TR, suggesting that, in this context, moderate TR can be treated conservatively and emphasizing the importance of TR quantitative assessment. In view of the observation, unencumbered by significant SPAP elevation by Doppler echocardiography or other comorbidity, of this very strong link to TR outcome, future studies should examine whether these strong conclusions can be applied to other well-defined subsets of patients with TR.

**STUDY LIMITATIONS.** Quantitation of TR performed as clinically required may cause selection bias but represents standard clinical practice. Doppler echocardiography to assess systolic pulmonary pressure in

the presence of severe TR may be questioned but is reliable to exclude likely pulmonary hypertension (36) and is part of present guidelines (17). Atrial fibrillation is frequent in isolated TR (14), but was carefully matched among TR groups and does not affect the TR impact on outcome. The comprehensive multivariate mortality analysis is potentially overfitted, which may result in lower predictive performance. At the time of patient enrollment, routine RV assessment did not include the tricuspid annular plane systolic excursion, Doppler-derived tricuspid lateral annular systolic velocity (S′), or 3-dimensional RV ejection fraction, the prognostic value of which will warrant prospective studies of isolated TR in the future. Affirming isolated functional TR requires comprehensive imaging of the tricuspid valve, which may be facilitated by up-to-date 3-dimensional imaging software. Magnetic resonance imaging is particularly suited for analyzing RV function but could not be implemented systematically. Future studies using combined imaging with magnetic resonance imaging or new 3-dimensional imaging software to assess RV in isolated functional TR quantified by Doppler echocardiography will be essential to provide combined RV and TR assessment (22). Guidelines do not provide class I indications for surgery of isolated, even severe, functional TR (2), and few patients were referred for surgery. We believe that our data support the rationale to consider surgery for severe isolated functional TR and more generally severe TR, even if not associated with left-sided valve diseases. Nevertheless, a clinical trial should be conducted to affirm the impact of tricuspid surgery on outcome.

## CONCLUSIONS

Isolated functional TR may be severe or even massive. Such patients, despite a benign appearance, have a poor outcome when TR is severe with excess mortality and high morbidity. Awareness of the condition is low and echocardiographic detection of severe, isolated TR, although best done with quantitative methods, should take advantage of all information available. Hence, this condition requires active detection by Doppler echocardiography and quantification of the severity of TR and should be closely monitored.

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