ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.09.036

Impact of Tricuspid Regurgitation on Long-Term Survival

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OBJECTIVES The goal of this study was to examine mortality associated with tricuspid regurgitation (TR) after controlling for left ventricular ejection fraction (LVEF), right ventricular (RV) dilation and dysfunction, and pulmonary artery systolic pressure (PASP).

BACKGROUND Tricuspid regurgitation is a frequent echocardiographic finding; however, the association with prognosis is unclear.

METHODS We retrospectively identified 5,223 patients (age 66.5 ± 12.8 years; predominantly male) undergoing echocardiography at one of three Veterans Affairs Medical Center laboratories over a period of four years. Follow-up data were available for four years (mean 498 ± 402 days). Kaplan-Meier and proportional hazards methods were used to compare differences in survival among TR grades.

RESULTS Mortality increased with increasing severity of TR. The one-year survival was 91.7% with no TR, 90.3% with mild TR, 78.9% with moderate TR, and 63.9% with severe TR. Moderate or greater TR was associated with increased mortality regardless of PASP (hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.16 to 1.49 for PASP >40 mm Hg; HR 1.32, 95% CI 1.05 to 1.62 for PASP ≤40 mm Hg) and LVEF (HR 1.49, 95% CI 1.34 to 1.66 for EF <50%; HR 1.54, 95% CI 1.37 to 1.71 for EF ≥50%). When adjusted for age, LVEF, inferior vena cava size, and RV size and function, survival was worse for patients with moderate (HR 1.17, 95% CI 0.96 to 1.42) and severe TR (HR 1.31, 95% CI 1.05 to 1.66) than for those with no TR.

CONCLUSIONS We conclude that increasing TR severity is associated with worse survival in men regardless of LVEF or pulmonary artery pressure. Severe TR is associated with a poor prognosis, independent of age, biventricular systolic function, RV size, and dilation of the inferior vena cava. (J Am Coll Cardiol 2004;43:405–9) © 2004 by the American College of Cardiology Foundation

Tricuspid regurgitation (TR) is a common echocardiographic finding that is present in 80% to 90% of normal individuals (1). Data on mortality in patients with other TR etiologies and severity are limited. We designed this study to examine mortality associated with TR after controlling for left ventricular ejection fraction (LVEF), right ventricular (RV) dilation and dysfunction, and pulmonary artery systolic pressure (PASP). We wished to test the hypothesis that moderate or greater TR adversely impacts survival, independent of pulmonary artery pressure and LVEF.

METHODS

Patient selection. We evaluated 5,507 consecutive patients undergoing echocardiography at one of the three laboratories at the Palo Alto Veterans Affairs Heath Care System between August 1998 and July 2002. We excluded 284 patients because the severity of TR was not reported, resulting in a study sample of 5,223. We identified subgroups of patients with normal or high (>40 mm Hg) PASP (2) and patients with normal (≥50%) or reduced LVEF.

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Manuscript received December 13, 2002; revised manuscript received September 2, 2003, accepted September 16, 2003.

Outcome. Veterans Affairs data and the Social Security Death Index were used to determine survival after echocardiography. Patients not known to have died were censored at the date of their last clinic or clinical laboratory visit. This study was approved by the Administrative Panel on Human Subjects in Medical Research at Stanford University.

Echocardiographic examination. A complete echocardiographic examination was performed for routine clinical evaluation, including two-dimensional, pulsed-wave, continuous-wave, and color Doppler imaging (Agilent Sonos 5500, 2500, and 1500 ultrasound systems). Continuous-wave Doppler was used to record flow and regurgitant jet signals in the apical four-chamber and RV inflow views.

Right ventricular size and function were qualitatively graded in the apical four-chamber and subcostal views. Tricuspid regurgitation was graded qualitatively using Framingham Heart Study criteria (1): mild if the regurgitant jet area/right atrial area was <19%; moderate if 20% to 40%; or severe if >41%. Enlargement of the RV was considered mild if the RV was greater than two-thirds of the LV but less than the LV size; moderate if the RV equaled the LV; and severe if the RV was greater than the LV (3). Right ventricular systolic function was estimated by the attending echocardiographer as normal or reduced, using the following criteria as a sign of RV dysfunction: 1) any RV wall motion abnormalities; and 2) descent of base <2.0 cm (4). Patients with moderate and severe RV enlargement were

Abbreviations and Acronyms

HR = hazard ratio
IVC = inferior vena cava
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
PASP = pulmonary artery systolic pressure
RV = right ventricle/ventricular
TR = tricuspid regurgitation

combined, as there were <20 patients with severe RV enlargement.

Right atrial pressure was estimated by visualizing the inferior vena cava (IVC) and its response to respiration. Right atrial pressure was estimated as 5 mm Hg if the IVC was <2.0 cm in diameter at the junction of the right atrium, 15 mm Hg if the IVC was dilated and collapsed with respiration, and 20 mm Hg if the IVC was dilated and did not collapse with respiration. Estimated PASP was calculated as the sum of tricuspid jet gradient and estimated right atrial pressure (5,6).

Statistical analysis. The software JMP version 3.1 (SAS Institute, Cary, North Carolina) was used for statistical analysis. A two-sided p value <0.05 was considered significant. Kaplan-Meier curves using the log-rank test were generated to determine the association between the severity of TR and survival. When groups were compared, analysis of variance was used for continuous variables, and the chi-square test was used for categorical variables. Indicators (dummy variables) were assigned to categorical variables (yes/no) for calculation of mortality hazard ratios (HRs), using univariate proportional hazards regression analyses. Proportional hazards methods were also used to adjust the TR hazard for RV size and function, LVEF, and age. A second analysis was performed that also controlled for pulmonary artery pressure in those with an adequate TR signal. The co-variates were removed stepwise until only those significant at $p < 0.05$ remained.

RESULTS

There were 601 patients (11.5%) with no TR, 3,805 (68.8%) with mild TR, 620 (11.8%) with moderate TR, and 199 (3.8%) with severe TR. The majority of patients were male (98%), and the patients' mean age was 66.5 ± 12.8 years (range 20 to 95). Sixty-four patients had primary tricuspid valve pathology, 45 had a mildly thickened valve, 7 had a moderately thickened valve, 8 had an annuloplasty ring, and 4 had a bioprosthetic valve.

Table 1 shows the characteristics of patients graded by TR severity. Patients with moderate or severe TR were older and had worse ventricular function than those with less TR.

Survival analysis. A total of 815 (15.6%) patients died (Table 2) during a mean follow-up period of 498 ± 402 days. The one-year survival rates for patients were 91.7% with no TR, 90.3% with mild TR, 78.9% with moderate TR, and 63.9% with severe TR (Fig. 1). Univariate analysis indicated that TR, RV dilation, reduced RV function, LVEF, pulmonary artery pressure, and IVC dilation were individually associated with higher mortality (Table 2).

Figures 2A and 2B shows the relationship between severity of TR and mortality for patients with high (>40 mm Hg) and normal (≤40 mm Hg) PASP. Patients with moderate or greater TR had increased mortality compared with those with mild or less TR, irrespective of PASP (HR 1.31, 95% confidence interval [CI] 1.16 to 1.49 for PASP >40 mm Hg; HR 1.32, 95% CI 1.05 to 1.62 for PASP ≤40 mm Hg).

Mortality also increased with increasing severity of TR in patients with a low EF (<50%) and normal EF (Figs. 3A and 3B). Moderate or greater TR was associated with increased mortality, regardless of LVEF (HR 1.49, 95% CI 1.34 to 1.66 for EF <50%; HR 1.54, 95% CI 1.37 to 1.71 for EF ≥50%), when compared with mild or less TR.

Moreover, the proportional hazards method showed that patients with moderate (HR 1.17, 95% CI 0.96 to 1.42) and severe TR (HR 1.31, 95% CI 1.05 to 1.66) had a worse prognosis than those with no TR after adjustment for age, LVEF, IVC size, RV size, and RV function (Table 3). In a subset of patients with TR and measured pulmonary artery pressure, only TR (severe vs. mild: HR 1.23, 95% CI 1.03 to 1.47; moderate vs. mild: HR 1.08, 95% CI 0.95 to 1.23), pulmonary artery pressure and age were associated with increased mortality. The results were not significantly changed by excluding patients with abnormal tricuspid morphology (n = 52) or an annuloplasty ring/bioprosthetic valve (n = 12).

Table 1. Clinical and Echocardiographic Features of Patients With Tricuspid Regurgitation

	No TR (n = 600)	Mild TR (n = 3,804)	Moderate TR (n = 620)	Severe TR (n = 199)	p Value
Age (yrs)	62.2 ± 12.8	66.0 ± 12.6	71.9 ± 11.7	71.9 ± 12.4	< 0.0001
LVEF (%)	57.3 ± 9.1	55.4 ± 11.6	47.1 ± 15.6	40.4 ± 17.2	< 0.0001
RV dilation	8%	11%	35%	66%	< 0.0001
RV dysfunction	3%	8%	30%	61%	< 0.0001
Dilated IVC	6%	11%	44%	76%	< 0.0001

Data are presented as the mean value ± SD or percentage of patients.
IVC = inferior vena cava; LVEF = left ventricular ejection fraction; RV = right ventricular; TR = tricuspid regurgitation.

Table 2. Mortality Versus Echocardiographic Findings by Univariable Proportional Hazards Analysis

Variable	n	Deaths (%)	Hazard Ratio (95% CI)	p Value
TR				
None	600	61 (10)	1.0	
Mild	3,804	499 (13)	1.12 (0.98–1.28)	0.09
Moderate	620	171 (28)	1.67 (1.45–1.94)	< 0.0001
Severe	199	84 (42)	2.20 (1.83–2.55)	< 0.0001
RV enlargement				
None	4,408	610 (14)	1.0	
Mild	665	143 (22)	1.29 (1.12–1.41)	< 0.0001
Moderate and severe	144	62 (43)	1.94 (1.69–2.20)	< 0.0001
RV dysfunction				
None	4,596	623 (14)	1.0	
Present	614	190 (31)	1.62 (1.49–1.75)	< 0.0001
IVC dilation				
None	3,350	389 (12)	1.0	
Dilated	519	125 (24)	1.54 (1.39–1.70)	< 0.0001
Dilated (without collapse)	184	77 (42)	2.09 (1.85–2.36)	< 0.0001
PASP*				
<40 mm Hg	1,360	136 (10)	1.0	
≥40 mm Hg	935	265 (28)	1.82 (1.65–2.02)	< 0.0001
Ejection fraction				
>50%	3,901	496 (13)	1.0	
<50%	1,306	314 (24)	1.42 (1.32–1.52)	< 0.0001

*Pulmonary artery systolic pressure (PASP) was available in patients with an adequate tricuspid regurgitation (TR) envelope.
CI = confidence interval; other abbreviations as in Table 1.

DISCUSSION

Tricuspid regurgitation is a common echocardiographic finding (1) that is often considered benign unless associated with significant pulmonary hypertension or RV or LV dysfunction (7,8). Our study confirms that mild or less TR does not affect the outcome.

However, moderate or greater TR was associated with a worse prognosis, even in the absence of ventricular dysfunction or pulmonary hypertension. Identification of risk factors for death is important for guidance of therapy, assignment of health care resources, and counseling of patients. Both decreased LV systolic function and elevated PASP are well-known markers of decreased survival (9). Because pulmonary hypertension and LV dysfunction, through secondary RV failure, may cause TR, we evaluated separate patient cohorts with normal and high PASP and normal and low LVEF. We found that patients with moderate or greater TR have worse survival than patients with mild or less TR, regardless of pulmonary artery pressure and LVEF. Based on these findings, significant (moderate or greater) TR should be considered an additional risk factor for mortality.

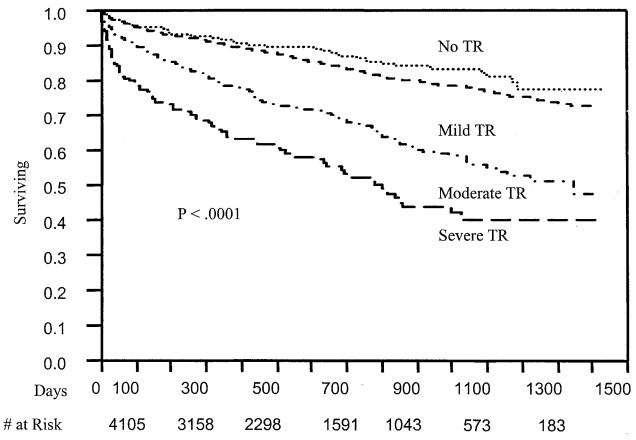

Figure 1. Kaplan-Meier survival curves for all patients with tricuspid regurgitation (TR). Survival is significantly worse in patients with moderate and severe TR.

Previous studies have shown that an enlarged RV is associated with increased mortality (10). Our findings show that increasing grades of TR are commonly associated with RV dilation and dysfunction and elevated right atrial pressure, as measured by IVC dilation. However, RV and atrial abnormalities only partially explain the association between moderate or greater TR and mortality observed in our study.

The reason for higher mortality with significant TR remains to be determined. It is possible that TR is a more sensitive marker of RV dysfunction than is visual interpretation of systolic performance. Also, the presence of TR may mask the decreased contractility of the RV, analogous to the effect of mitral regurgitation on the ability to estimate LV contractility from LVEF. Future studies should exam-

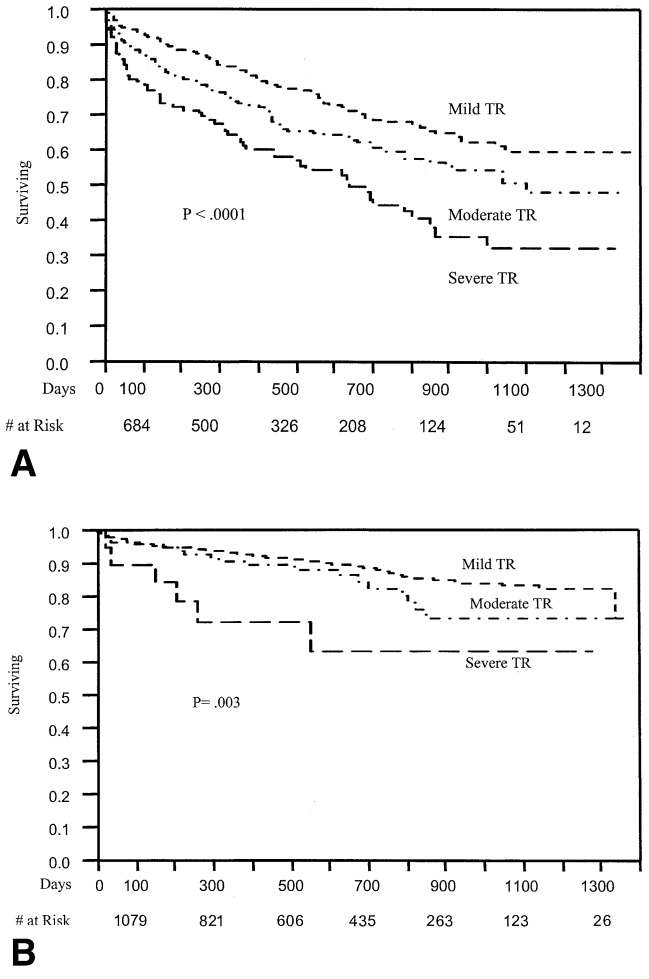

Figure 2. Kaplan-Meier survival curves for **(A)** patients with tricuspid regurgitation (TR) and high pulmonary artery systolic pressure (≥40 mm Hg) and **(B)** patients with TR and normal pulmonary artery systolic pressure (<40 mm Hg).

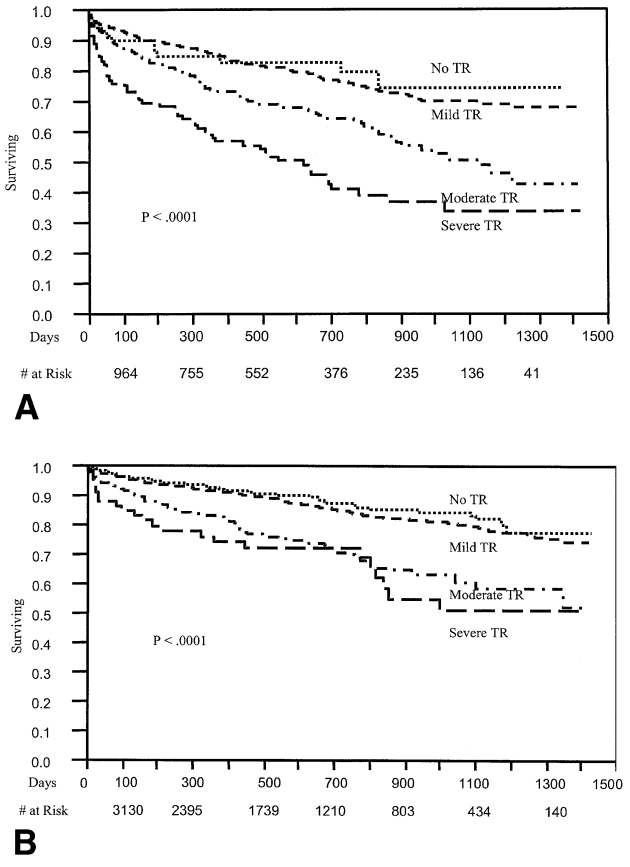

Figure 3. Kaplan-Meier survival curve for **(A)** patients with tricuspid regurgitation (TR) and a low left ventricular ejection fraction (<50%) and **(B)** patients with TR and a normal left ventricular ejection fraction (≥50%).

ine the cause of death in patients with significant TR to better determine the reason for the association of TR with mortality.

Study limitations. Most of the patients were men, and these data may not be applicable to female patients. The criteria for quantification of TR are largely subjective, and quantitative analysis of TR using proximal isovelocity surface area and jet width methods (11) may have been helpful. Clinical characteristics, including the patients' functional class and the effect of specific treatments, were unknown at the time of echocardiography. Finally, the causes of death were not identified. Median follow-up was 428 days; however, follow-up was available for 584 patients for more than three years. In addition, interobserver variability is unknown and, if substantial, would make it difficult to detect differences in outcome between patients groups. We relied on the presence of an adequate TR envelope to estimate pulmonary artery pressure.

Conclusions. We conclude that increasing TR severity is associated with worse survival in men regardless of LVEF or pulmonary artery pressure. Severe TR is associated with a poor prognosis, independent of age, biventricular systolic function, RV size, and IVC dilation. Further studies are needed to better determine the mechanism responsible for the association between TR and increased mortality.

Table 3. Clinical and Echocardiographic Parameters Associated With Long-Term Survival*

Variable	Chi-Square	p Value
TR		
Mild	0.15	0.70
Moderate	2.65	0.10
Severe	5.79	0.02
Age	65.75	< 0.0001
LVEF	4.28	0.04
IVC		
Dilated	13.95	0.0002
Dilated without collapse	21.15	< 0.0001
RV enlargement		
Mild	0.90	0.34
Moderate and severe	4.05	0.04
RV dysfunction	2.12	0.14

*Using a proportional hazards model.
Abbreviations as in Table 1.

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