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STRUCTURAL

Tricuspid Regurgitation Is Associated With Increased Risk of Mortality in Patients With Low-Flow Low-Gradient Aortic Stenosis and Reduced Ejection Fraction

Results of the Multicenter TOPAS Study (True or Pseudo-Severe Aortic Stenosis)

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ABSTRACT

OBJECTIVES This study sought to examine the impact of tricuspid regurgitation (TR) on mortality in patients with low-flow, low-gradient (LF-LG) aortic stenosis (AS) and reduced left ventricular ejection fraction (LVEF).

BACKGROUND TR is often observed in patients with LF-LG AS and low LVEF, but its impact on prognosis remains unknown.

METHODS A total of 211 patients (73 ± 10 years of age; 77% men) with LF-LG AS (mean gradient <40 mm Hg and indexed aortic valve area [AVA] ≤0.6 cm^2/m^2) and reduced LVEF (≤40%) were prospectively enrolled in the TOPAS (True or Pseudo-Severe Aortic Stenosis) study and 125 (59%) of them underwent aortic valve replacement (AVR) within 3 months following inclusion. The severity of AS was assessed by the projected AVA (AVA_{proj}) at normal flow rate (250 ml/s), as previously described and validated. The severity of TR was graded according to current guidelines.

RESULTS Among the 211 patients included in the study, 22 (10%) had no TR, 113 (54%) had mild (grade 1), 50 (24%) mild-to-moderate (grade 2), and 26 (12%) moderate-to-severe (grade 3) or severe (grade 4) TR. During a mean follow-up of 2.4 ± 2.2 years, 104 patients (49%) died. Univariable analysis showed that TR ≥2 was associated with increased risk of all-cause mortality (hazard ratio [HR]: 1.82, 95% confidence interval [CI]: 1.22 to 2.71; p = 0.004) and cardiovascular mortality (HR: 1.85, 95% CI: 1.20 to 2.83; p = 0.005). After adjustment for age, sex, coronary artery disease, AVA_{proj}, LVEF, stroke volume index, right ventricular dysfunction, mitral regurgitation, and type of treatment (AVR vs. conservative), the presence of TR ≥2 was an independent predictor of all-cause mortality (HR: 1.88, 95% CI: 1.08 to 3.23; p = 0.02) and cardiovascular mortality (HR: 1.92, 95% CI: 1.05 to 3.51; p = 0.03). Furthermore, in patients undergoing AVR, TR ≥3 was an independent predictor of 30-day mortality compared with TR = 0/1 (odds ratio [OR]: 7.24, 95% CI: 1.56 to 38.2; p = 0.01) and TR = 2 (OR: 4.70, 95% CI: 1.00 to 25.90; p = 0.05).

CONCLUSIONS In patients with LF-LG AS and reduced LVEF, TR is independently associated with increased risk of cumulative all-cause mortality and cardiovascular mortality regardless of the type of treatment. In patients undergoing AVR, moderate/severe TR is associated with increased 30-day mortality. Further studies are needed to determine whether TR is a risk marker or a risk factor of mortality and whether concomitant surgical correction of TR at the time of AVR might improve outcomes for this high-risk population. (J Am Coll Cardiol Intv 2015;8:588–96) © 2015 by the American College of Cardiology Foundation.

Patients with low-flow, low-gradient (LF-LG) aortic stenosis (AS) and reduced left ventricular ejection fraction (LVEF) have a poor prognosis with conservative therapy but a high operative mortality with aortic valve replacement (AVR) (1-7). Risk stratification is essential in these patients to optimize therapeutic management and outcomes. Previous studies have reported that multivessel coronary artery disease, mean gradient <20 mm Hg, absence of LV flow reserve on dobutamine stress echocardiography, peak stress LVEF <35%, and more severe stenosis on dobutamine stress echocardiography are associated with worse outcomes in patients with LF-LG AS (2-5,8).

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Functional tricuspid regurgitation (TR) is a common finding in patients with left-sided heart valve diseases (9-15). Several studies have reported an increased risk of mortality in chronic heart failure patients having moderate or severe TR (9,14,16,17). No data exist about the prevalence and prognosis of TR in patients with LF-LG AS. The objective of this study was to examine the impact of TR on mortality in patients with LF-LG AS and low LVEF.

METHODS

STUDY PROTOCOL. For the purpose of this study, we analyzed the data of patients prospectively recruited in the TOPAS (True or Pseudo-Severe Aortic Stenosis) multicenter prospective observational study (7,18). Between July 24, 2002 and March 1, 2012, 211 patients with LF-LG AS (mean gradient <40 mm Hg, indexed aortic valve area [AVA] $\leq$0.6 cm^2/m^2) with reduced LVEF ($\leq$40%) were recruited in 3 academic centers (Québec, Ottawa, and Vienna). Patients were excluded if they had greater than mild aortic regurgitation, greater than mild organic mitral regurgitation, or greater than mild mitral stenosis.

CLINICAL DATA. Clinical data included age, sex, height, weight, body surface area, systolic and diastolic blood pressure, New York Heart Association functional class, documented diagnosis of traditional cardiovascular risk factors and comorbidities such as hypertension, diabetes, dyslipidemia, smoking, and chronic obstructive pulmonary disease, coronary artery disease (history of myocardial infarction or $\geq$50% coronary artery stenosis on coronary angiography), and logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation). Medication was recorded at the time of echocardiography.

DOPPLER ECHOCARDIOGRAPHY. At baseline, all patients underwent comprehensive echocardiography at rest and during dobutamine stress echocardiography as previously described (18). LVEF was measured by the biplane Simpson method. Stroke volume was measured in the LV outflow tract and indexed for body surface area. AVA was measured using the continuity equation. AS severity was assessed using the projected AVA at a normal transvalvular flow rate (AVA_{proj}) (18,19).

The severity of TR was assessed using an integrated approach and graded as none (0), mild (grade 1), mild-to-moderate (grade 2), moderate-to-severe (grade 3), and severe (grade 4) according to current guidelines (20-22). Tricuspid annulus diameter was measured at end diastole from a right ventricle-focused apical 4-chamber view as recommended (23,24). Systolic

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVAproj = projected aortic valve area at normal flow rate

AVR = aortic valve replacement

CI = confidence interval

HR = hazard ratio

LF-LG = low-flow, low-gradient

LVEF = left ventricular ejection fraction

OR = odds ratio

RV = right ventricular

SVI = stroke volume index

TR = tricuspid regurgitation

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pulmonary arterial pressure was calculated by adding the peak TR systolic gradient and the estimated central venous pressure. Right ventricular (RV) function was assessed by an integrative approach and classified as normal or reduced (25).

STATISTICAL ANALYSIS. Results are expressed as mean ± SD or percents unless otherwise specified. Differences between patients in different groups were compared with the use of 1-way analysis of variance and Tukey test for continuous variables and the chi-square test for categorical variables. Kaplan-Meier curves and log-rank test of the time-to-event data were used to assess the effect of TR on mortality. The effect of the clinical and Doppler-echocardiographic variables on survival was assessed with the use of Cox proportional hazard regression models for cumulative all-cause mortality and with backward stepwise logistic regression analysis for 30-day mortality in the subset of patients undergoing AVR. The proportional hazards assumption was checked with the use of Schoenfeld residuals. All the variables with a p value of <0.10 in univariable analysis and those with clinical relevance regardless of their level of significance (i.e., age, sex, systolic pulmonary arterial pressure and type of treatment [AVR vs. conservative]) were incorporated in the multivariable models. Further adjustment for classical echocardiographic parameters of LV systolic function (i.e., LVEF and stroke volume index [SVI]) and RV systolic function was performed. A p value <0.05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS. Patient characteristics are shown in Table 1. Among the 211 patients included in this study (mean age: 73 ± 10 years; 77%, n = 163 male), 108 (51%) were classified as New York Heart Association functional class III or greater. One hundred and twenty-five patients (59%) underwent AVR within 3 months of enrollment and the remaining patients (n = 86, 41%) were treated conservatively. Among patients undergoing AVR, 99 (79%) were treated surgically (55 with concomitant coronary artery bypass graft surgery and 3 with concomitant tricuspid valve annuloplasty) and 26 (21%) were treated by transcatheter procedure.

There were 22 patients (10%) with no TR, 113 (54%) with grade 1, 50 (24%) with grade 2, and 26 (12%) with grade 3 or 4 (3/4) TR. Patients with TR = 3/4 had similar baseline demographics and prevalence of cardiovascular risk factors as did those with TR = 2 or those with TR = 0/1 (Table 1), except for diabetes, which was more prevalent (p = 0.01) in patients with TR = 3/4. Regarding Doppler echocardiographic data, AVA was significantly smaller in patients with TR but mean gradient and projected AVA were similar among groups (Table 1). Patients with TR had significantly lower LVEF (p = 0.02), lower SVI (p < 0.0001), higher prevalence of secondary mitral regurgitation (p = 0.001), and larger tricuspid annulus diameter (p < 0.0001). Patients with TR = 3/4 had higher prevalence of reduced RV function than did those with TR = 0/1 and those with TR = 2 (Table 1).

IMPACT OF TRICUSPID REGURGITATION ON MORTALITY. During a mean follow-up of 2.4 ± 2.2 years, 104 patients (49%) died (87 deaths [84%] were from cardiovascular causes) resulting in 2- and 4-year survival rates of 65 ± 3% and 48 ± 4%, respectively. Patients with TR ≥2 had significantly lower 2- and 4-year survival rates (Figure 1A) than did those with TR = 0/1 (50 ± 6% vs. 73 ± 4% and 30 ± 6% vs. 58 ± 5%; log-rank: p = 0.003, respectively). The patients with TR = 1 had similar survival as those with no TR (4-year survival: 55 ± 10% vs. 58 ± 6%; p = 0.32).

Univariable analysis showed that TR ≥2 was associated with increased risk of all-cause mortality (hazard ratio [HR]: 1.82, 95% confidence interval [CI]: 1.22 to 2.71; p = 0.004) as well as of cardiovascular mortality (HR: 1.85, 95% CI: 1.20 to 2.83; p = 0.005). After adjustment for type of treatment (AVR vs. conservative), TR ≥2 remained associated with increased risk of all-cause mortality (HR: 1.99, 95% CI: 1.32 to 2.98; p = 0.001) (Table 2) and cardiovascular mortality (HR: 2.03, 95% CI: 1.31 to 3.12; p = 0.001). In multivariable Cox proportional hazard model adjusted for age, sex, coronary artery disease, diabetes, AVA_{proj}, LVEF, SVI, systolic pulmonary arterial pressure, mild or greater secondary mitral regurgitation and type of treatment, the presence of TR ≥2 was an independent predictor of all-cause mortality (HR: 1.91, 95% CI: 1.13 to 3.26; p = 0.01) (Table 2) and cardiovascular mortality (HR: 1.92, 95% CI: 1.05 to 3.51; p = 0.03). There was a graded relationship between TR severity and the tricuspid annulus diameter (Figure 2). However, the independent association between TR and all-cause mortality persisted after further adjustment for tricuspid annulus diameter (HR: 1.91, 95% CI: 1.04 to 3.53; p = 0.03) or RV dysfunction (HR: 1.88, 95% CI: 1.08 to 3.23; p = 0.02).

Patients with TR = 3/4 had significant lower 2-year survival (Figure 1B) than did those with TR = 2 and those with TR = 0/1 (41 ± 10% vs. 56 ± 8% and 73 ± 4%; p = 0.005, respectively). Additional analyses

TABLE 1 Baseline Clinical and Doppler Echocardiographic Characteristics of the Study Population

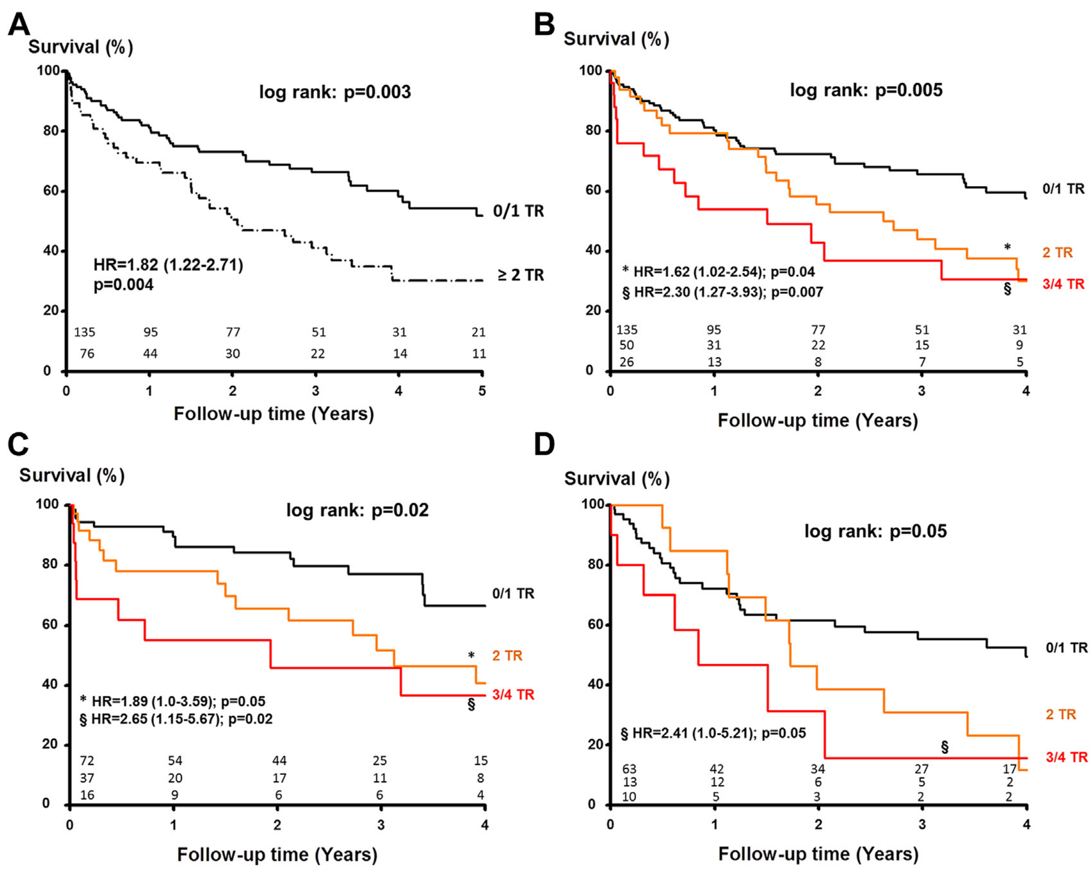
	Whole Cohort (N = 211)	Grade 0/1 TR (n = 135; 64%)	Grade 2 TR (n = 50; 24%)	Grade 3/4 TR (n = 26; 12%)	p Value
Demographics and physical exam					
Age, yrs	73.0 ± 10.0	71.6 ± 10.0	74.7 ± 10.0	72.3 ± 9.6	0.2
Male	163 (77)	107 (79)	36 (72)	20 (77)	0.6
Body surface area, m^2	1.84 ± 0.21	1.86 ± 0.21	1.82 ± 0.23	1.82 ± 0.18	0.8
Systolic blood pressure, mm Hg	120 ± 18	122 ± 18	118 ± 17	117 ± 18	0.2
Diastolic blood pressure, mm Hg	72 ± 10	73 ± 10	70 ± 11	73 ± 9	0.4
NYHA functional class ≥III	108 (51)	67 (50)	28 (56)	13 (50)	0.8
Risk factors and concomitant diseases					
Hypertension	136 (64)	88 (65)	31 (62)	17 (65)	0.9
Diabetes	74 (35)	43 (32)	15 (30)	16 (62)*	0.01
Dyslipidemia	148 (70)	92 (68)	36 (72)	20 (77)	0.7
Smoking	125 (59)	74 (55)	33 (66)	18 (69)	0.3
Coronary artery disease	136 (64)	88 (65)	37 (74)	19 (73)	0.7
Coronary artery bypass graft	74 (35)	37 (27)	15 (30)	7 (27)	0.9
Previous myocardial infarction	110 (52)	69 (51)	25 (50)	16 (62)	0.6
Chronic obstructive pulmonary disease	60 (28)	35 (26)	15 (30)	10 (38)	0.4
Logistic EuroSCORE, %	23.5 ± 18.5	21.9 ± 18.3	25.4 ± 20.3	27.3 ± 16.7	0.5
Medication					
Beta-blockers	131 (62)	87 (64)	28 (56)	16 (62)	0.8
Diuretic agents	148 (70)	87 (64)†	39 (78)	22 (85)	0.03
ACEI/ARB	121 (57)	81 (60)	27 (54)	13 (50)	0.5
Statins	128 (60)	79 (58)	31 (62)	18 (69)	0.5
Doppler echocardiographic data					
LV end-diastolic diameter, mm	58 ± 10	59 ± 11	58 ± 8	57 ± 8	0.5
LV end-systolic diameter, mm	48 ± 10	48 ± 11	48 ± 9	48 ± 9	0.9
Left atrial diameter, mm	45 ± 9	46 ± 10	44 ± 9	46 ± 5	0.6
LV stroke volume, ml	57 ± 17	61 ± 18†	52 ± 13	45 ± 13	<0.0001
LV stroke volume index, ml/m^2	31 ± 9	33 ± 9†	29 ± 6	24 ± 6	<0.0001
LV ejection fraction, %	29 ± 9	29 ± 9	29 ± 6	24 ± 8*	0.02
Mitral regurgitation > mild	23 (11)	7 (5)†	9 (18)	7 (27)	0.001
Tricuspid annulus diameter, mm	41 ± 7	39 ± 6	42 ± 8	48 ± 6*	<0.0001
Systolic pulmonary arterial pressure, mm Hg	46 ± 13	44 ± 12	47 ± 15	52 ± 12	0.12
Reduced RV systolic function	108 (51)	61 (45)	27 (54)	20 (77)*	0.02
Mean transvalvular gradient, mm Hg	24 ± 9	24 ± 8	25 ± 9	24 ± 7	0.5
Aortic valve area, cm^2	0.84 ± 0.24	0.88 ± 0.22†	0.77 ± 0.23	0.73 ± 0.26	0.0006
Projected aortic valve area, cm^2	1.02 ± 0.21	1.04 ± 0.20	0.99 ± 0.20	1.03 ± 0.30	0.5

Values are mean ± SD or n (%). *p < 0.05 for grade 3/4 versus 0/1 and 2. †p < 0.05 for grade 0/1 versus 2 and 3/4.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LV = left ventricular; NYHA = New York Heart Association; RV = right ventricular; TR = tricuspid regurgitation.

according to the type of treatment showed that TR severity was associated with increased risk of mortality in both patients treated with AVR (p = 0.02) (Figure 1C) and those treated conservatively (p = 0.05) (Figure 1D). Univariable Cox regression analysis showed that patients with TR = 2 (HR: 1.62, 95% CI: 1.02 to 2.54; p = 0.04) and those with TR = 3/4 (HR: 2.30, 95% CI: 1.27 to 3.93; p = 0.007) (Table 3) had increased risk of mortality than did those with TR = 0/1. After adjustment for type of treatment (AVR vs. conservative), presence of TR = 2 (HR: 1.76, 95% CI: 1.10 to 2.77; p = 0.02) and TR = 3/4 (HR: 2.34, 95% CI: 1.27 to 4.07; p = 0.008) (Table 3) were significantly associated with increased risk of all-cause mortality. After further adjustment for other risk factors, TR = 2 (HR: 2.19, 95% CI: 1.00 to 4.77; p = 0.05) and TR = 3/4 (HR: 2.68, 95% CI: 1.08 to 6.32; p = 0.03) (Table 3) remained significantly associated with increased risk of all-cause mortality.

There was no significant interaction between the center where the patient was recruited (i.e., Québec, Ottawa, or Vienna) and TR with respect to impact on mortality. Furthermore, in hierarchical multivariable analysis including the center, TR remained

FIGURE 1 **Impact of TR on All-Cause Mortality for the Whole Cohort**



The survival rates for the whole cohort (N = 211) according to the grade of tricuspid regurgitation (TR) (grade 0/1 vs. grade ≥2 **[A];** grade 0/1 vs. grade 2 vs. grade 3/4 **[B]**) are shown. **(C)** The survival rates are shown for the patients treated with aortic valve replacement according to the severity of TR. **(D)** The survival rates are shown for the patients treated conservatively according to TR severity. *Hazard ratio (HR) and p value for TR = 2 versus TR = 0/1; §HR and p value for TR = 3/4 versus TR = 0/1. The numbers at the bottom of the graph represent the number of patients at risk at each follow-up year.

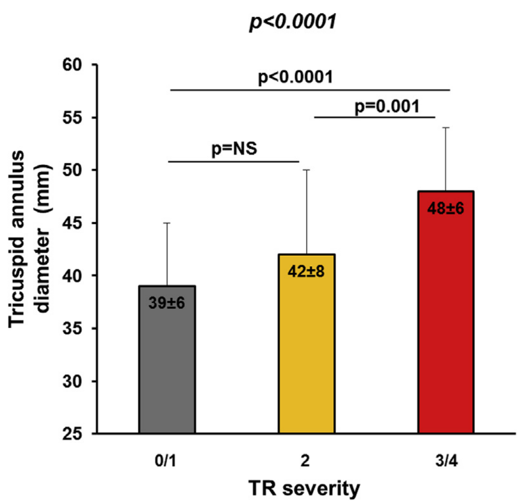
significantly associated with mortality (TR ≥2: HR: 2.53, 95% CI: 1.41 to 4.56; p = 0.002).

IMPACT OF TRICUSPID REGURGITATION ON 30-DAY MORTALITY IN PATIENTS TREATED BY AVR. Among patients who underwent AVR (n = 125), there were 16 patients with TR = 3/4 and 37 with TR = 2. Fifteen patients died following AVR resulting in 30-day mortality of 12%. Six deaths (37.5%) occurred in the group of patients with TR = 3/4 compared with 4 (10.8%) in those with TR = 2, and 5 (6.9%) in those with TR = 0/1 ($p < 0.05$) (Figure 3).

Univariable logistic regression analysis showed that TR = 3/4 was associated with increased risk of 30-day mortality compared with TR = 0/1 (odds ratio [OR]: 8.04, 95% CI: 2.07 to 33.06; p = 0.003) and TR = 2 (OR: 4.95, 95% CI: 1.19 to 22.06; p = 0.028). However, TR = 2 was not associated with increased risk of 30-day mortality (OR: 1.62, 95% CI: 0.38 to 6.53; p = 0.49). In multivariable logistic regression, TR = 3/4 was an independent predictor of 30-day mortality compared with TR = 0/1 (OR: 7.24, 95% CI: 1.56 to 38.2; p = 0.01) and TR = 2 (OR: 4.70, 95% CI: 1.00 to 25.90; p = 0.05).

AVR was nonetheless associated with reduced risk of mortality in univariable analysis (HR: 0.62, 95% CI: 0.41 to 0.91; p = 0.015) as well as in multivariable analysis after adjustment for clinical risk factors and echocardiographic parameters of AS severity, LV dysfunction, RV dysfunction, and

FIGURE 2 Relationship Between Tricuspid Annulus Diameter and TR Severity



The graph shows the relationship between tricuspid annulus diameter and tricuspid regurgitation (TR) severity.

TR severity (HR: 0.42, 95% CI: 0.20 to 0.87; p = 0.019).

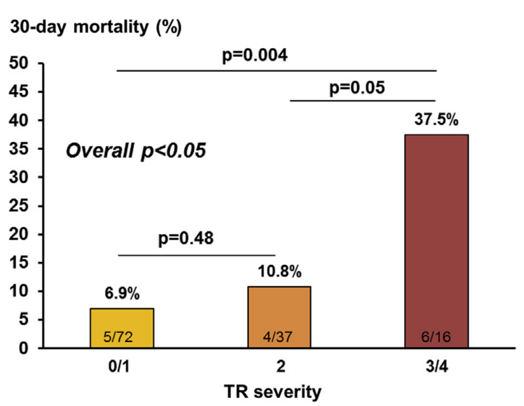
DISCUSSION

There are 3 main findings of the present study: 1) TR is independently associated with increased risk of cumulative all-cause mortality and cardiovascular mortality in patients with low LVEF, LF-LG AS; 2) there is a graded association between TR severity and increased risk of mortality; and 3) moderate/severe TR is independently associated with increased risk of 30-day mortality following AVR.

TR AND LATE OUTCOMES IN LF-LG AS. In the present study, TR was associated with increased risk of mortality independently of comorbidities, LV function, AS severity, mitral regurgitation severity, and type of treatment (AVR vs. conservative). Furthermore, mortality risk increased with the severity of TR. These findings are consistent with those previously published (16,17) in patients with chronic heart failure where moderate/severe TR was associated with increased risk of mortality.

TR can contribute to reduced LV outflow (forward stroke volume), which has been shown to be a strong predictor of mortality in patients with AS (26,27). Accordingly, our patients with more severe TR had

FIGURE 3 Impact of TR on 30-Day Mortality



The graph shows the impact of tricuspid regurgitation (TR) on perioperative (30-day) mortality in the subset of patients who underwent aortic valve replacement.

TABLE 2 Impact of TR (Grade ≥2) on All-Cause Mortality

	HR	95% CI	p Value
Unadjusted analysis	1.82	1.22–2.71	0.004
Analysis adjusted for			
Type of treatment (AVR vs. conservative)	1.99	1.32–2.98	0.001
Type of treatment, age, sex, CAD, diabetes, AVA_{proj}, LVEF, SVI, SPAP, and MR	1.91	1.13–3.26	0.01
Type of treatment, age, sex, CAD, diabetes, AVA_{proj}, LVEF, SVI, SPAP, MR, and RV dysfunction	1.88	1.08–3.23	0.02

AVA_{proj} = projected aortic valve area at normal flow rate; AVR = aortic valve replacement; CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; SPAP = systolic pulmonary arterial pressure; SVI = stroke volume index; other abbreviations as in Table 1.

TABLE 3 Impact of TR Severity on All-Cause Mortality

	TR Grade	HR	95% CI	p Value
Unadjusted analysis	0/1	Ref.	–	–
	2	1.62	1.02–2.54	0.04
	3/4	2.30	1.27–3.93	0.007
Analysis adjusted for				
Type of treatment (AVR vs. conservative)	0/1	Ref.	–	–
	2	1.76	1.10–2.77	0.02
	3/4	2.34	1.27–4.07	0.008
Type of treatment, age, sex, CAD, AVA_{proj}, LVEF, SVI, SPAP, MR, and RV dysfunction	0/1	Ref.	–	–
	2	2.19	1.00–4.77	0.05
	3/4	2.68	1.08–6.32	0.03

This table shows the impact of TR grade 2 or 3/4 versus 0/1 (referent group) on mortality.

Ref. = referent group; other abbreviations as in Tables 1 and 2.

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lower SVI. However, even after adjustment for SVI, TR remained independently associated with reduced survival.

Previous studies in patients undergoing left-sided valve surgery have reported that dilation of the tricuspid annulus is a powerful predictor of progressive TR even in patients with only mild secondary TR (25). In the present cohort, both patients with grade 2 TR and those with grades 3/4 TR had significant tricuspid annulus dilation (**Figure 2**). The association between the presence/severity of TR and mortality nonetheless persisted after adjustment for tricuspid annulus diameter.

The underlying mechanisms related to the higher mortality in patients with TR remain unclear. Previous studies (14,16) have shown that the presence of TR predicts RV dilation and dysfunction and is associated with worse survival. However in the study by Nath et al. (16), RV dysfunction explained only part of this association. In the latter study, the investigators hypothesized that TR may be a more sensitive marker of RV dysfunction than the visual assessment of RV systolic performance. In fact, the presence of TR may mask reduced RV contractility, in a similar way as mitral regurgitation limits the ability of LVEF to identify impaired LV contractility. In our study, TR remained associated with increased risk of mortality even after further adjustment for the presence of RV dysfunction.

TR AND 30-DAY MORTALITY IN LF-LG AS. In the subset of patients treated with AVR, our data showed that 30-day mortality was markedly higher in patients with TR than in those without TR. Boldt et al. (28) showed that in patients with severe AS, pre-operative RV dysfunction was associated with a greater occurrence of hemodynamic instability and greater requirement of post-operative inotropic support; however, they did not have the statistical power to analyze mortality. Our results extend these observations and strongly emphasize the importance of TR and associated RV dilation (tricuspid annular dilation) and dysfunction in patients with LF-LG AS and low LVEF.

In the present study, AVR was associated with improved late survival even after adjustment for other risk factors including TR. These findings are consistent with previous studies suggesting that AVR is protective in patients with low LVEF, LF-LG AS, including those with no LV contractile reserve (2,5,26). Hence, the presence of TR should not preclude consideration of AVR in patients with LF-LG AS.

CLINICAL IMPLICATIONS. The main clinical implication of this study is that presence and severity of TR should be systematically integrated in the risk stratification process of patients with LF-LG AS and reduced LVEF. The present study indeed shows that TR $\geq$2 is independently associated with 2-fold increased risk of mortality in these patients. This information would also lend support to the consideration of concomitant tricuspid annuloplasty in the subset of patients undergoing AVR. According to the 2012 European Society of Cardiology guidelines (25), tricuspid valve surgery is indicated (Class I; Level of Evidence: C) in patients with severe TR and should be considered (Class IIa; Level of Evidence: C) in patients with moderate primary TR as well as in patients with mild or moderate secondary TR and significant dilation of the tricuspid annulus ($\geq$40 mm or 21 mm/m^2) undergoing left-sided valve surgery. However, these recommendations are mainly on the basis of data arising from a small number of retrospective studies of patients requiring mitral valve replacement/repair for mitral stenosis. Hence, further studies are needed to determine the risk/benefit ratio of a concomitant tricuspid valve procedure in patients with LF-LG AS and low LVEF undergoing AVR. It indeed remains unclear whether the correction of a secondary TR in these patients would translate into better outcomes.

STUDY LIMITATIONS. The population size, albeit large for this clinical entity, may have limited our ability to detect significant associations with other risk factors in the total cohort, as well as in the subgroup of patients undergoing AVR.

It is possible that, due to the reduced RV function and low-flow state, the TR severity was underestimated in some patients included in this study, similar to what may occur in patients with secondary mitral regurgitation. Although RV function was qualitatively assessed by the cardiologist for each patient, the quantitative parameters of RV function (e.g., tricuspid annular plane systolic excursion, tricuspid annulus systolic velocity) were not systematically measured in this study and were available only in a small subset of patients. Further studies are needed to assess the respective impact of RV function and TR in patients with LF-LG AS.

CONCLUSIONS

In patients with LF-LG AS and reduced LVEF, TR is independently associated with increased risk of mortality. Increasing TR severity is associated with a greater risk of mortality. Furthermore, moderate/severe TR is independently associated with increased

30-day mortality in patients undergoing AVR. Hence, assessment of TR severity should be systematically integrated in the risk stratification and therapeutic decision making in patients with LF-LG AS and low LVEF. Further studies are needed to determine whether TR is a risk marker or risk factor for mortality and whether surgical correction of TR at the time of AVR improves outcomes in this high-risk population.

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PERSPECTIVES

WHAT'S KNOWN? TR is often observed in patients with LF-LG AS and low LVEF, but its impact on prognosis is unknown.

WHAT'S NEW? Among patients with LF-LG AS, those with TR grade ≥2 have a 2-fold increased risk of mortality. Furthermore, TR grade ≥3 is independently associated with increased 30-day mortality in the subset of patients undergoing AVR.

WHAT'S NEXT? The presence and severity of TR should be systematically integrated in the risk stratification process of patients with LF-LG AS and reduced LVEF. Further studies are needed to determine whether concomitant tricuspid annuloplasty would translate into better outcomes in the subset of patients undergoing AVR.

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