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Natural History of Functional Tricuspid Regurgitation Quantified by Cardiovascular Magnetic Resonance

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ABSTRACT

BACKGROUND Quantitation of tricuspid regurgitant (TR) severity can be challenging with conventional echocardiographic imaging and may be better evaluated using cardiovascular magnetic resonance (CMR).

OBJECTIVES In patients with functional TR, this study sought to examine the relationship between TR volume (TRVol) and TR fraction (TRF) with all-cause mortality.

METHODS We examined 547 patients with functional TR using CMR to quantify TRVol and TRF. The primary outcome was all-cause mortality. Thresholds for mild, moderate, and severe TR were derived based on natural history outcome data.

RESULTS During a median follow-up of 2.6 years (interquartile range: 1.7 to 3.3 years), there were 93 deaths, with an estimated 5-year survival of 79% (95% confidence interval [CI]: 73% to 83%). After adjustment of clinical and imaging variables, including RV function, both TRF (adjusted hazard ratio [AHR] per 10% increment: 1.26; 95% CI: 1.10 to 1.45; $p = 0.001$) and TRVol (AHR per 10-ml increment: 1.15; 95% CI: 1.04 to 1.26; $p = 0.004$) were associated with mortality. Patients in the highest-risk strata of TRVol ≥45 ml or TRF ≥50% had the worst prognosis (AHR: 2.26; 95% CI: 1.36 to 3.76; $p = 0.002$ for TRVol and AHR: 2.60; 95% CI: 1.45 to 4.66; $p = 0.001$ for TRF).

CONCLUSIONS This is the first study to use CMR to assess independent prognostic implications of functional TR. Both TRF and TRVol were associated with increased mortality after adjustment for clinical and imaging covariates, including right ventricular ejection fraction. A TRVol of ≥45 ml or TRF of ≥50% identified patients in the highest-risk strata for mortality. These CMR thresholds should be used for patient selection in future trials to determine if tricuspid valve intervention improves outcomes in this high-risk group. (J Am Coll Cardiol 2020;76:1291–301) © 2020 by the American College of Cardiology Foundation.

Significant tricuspid regurgitation (TR) affects 1.6 million patients in the United States and is independently associated with morbidity and mortality (1). More than 90% of significant TR cases are due to a functional etiology, which is not inherently a disease of the valve but, rather, the culmination of various disease processes (left-sided valve, myocardial disease, pulmonary hypertension, or atrial fibrillation) that lead to a combination of tricuspid annular dilation and tricuspid leaflet tethering from right ventricle (RV) remodeling (2–4).

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ABBREVIATIONS AND ACRONYMS

AHR = adjusted hazard ratio

BMA = Bayesian model averaging

CMR = cardiovascular magnetic resonance

IQR = interquartile range

LA = left atrium

LV = left ventricular

PA = pulmonary artery

RA = right atrium

RV = right ventricle

RVEF = right ventricular ejection fraction

SV = stroke volume

TR = tricuspid regurgitation

TRF = tricuspid regurgitant fraction

TRVol = tricuspid regurgitant volume

Although secondary TR portends a poor prognosis (5–9), there is equipoise regarding the role of isolated surgical intervention (10). Surgical management of isolated TR may not be better than medical therapy (11), and it carries the highest mortality of any valve intervention (12). This may be, in part, from the concomitant comorbidities of pulmonary hypertension and RV dysfunction. New percutaneous interventions are under development (13) that may reduce TR severity with lower procedural mortality. Therefore, accurate quantification of TR is now essential for patient selection and procedural follow-up.

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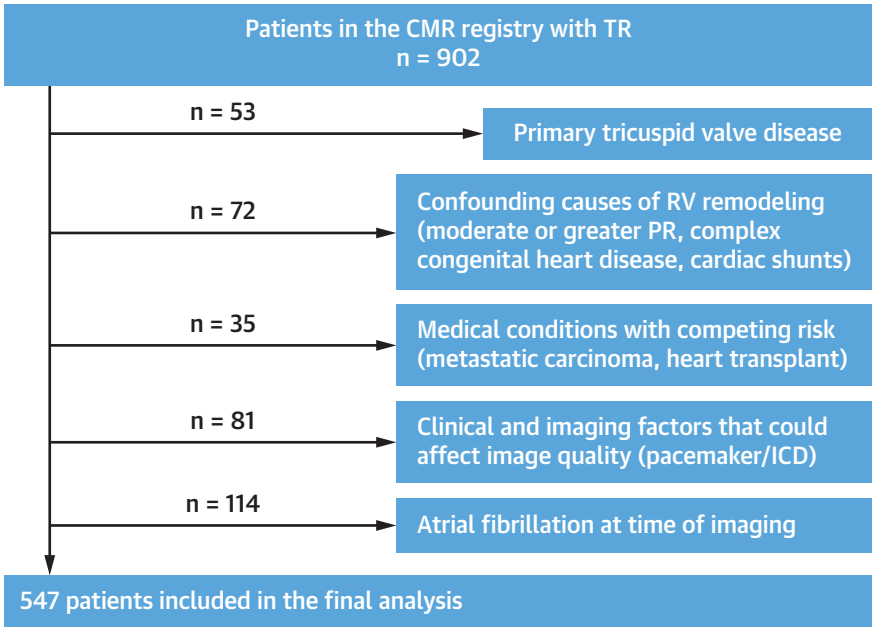
Conventionally, echocardiography has been used to quantify TR, but there are challenges (14) and limitations (15) with this imaging modality. Additionally, thresholds for severe TR have not been derived from natural history datasets but, rather, using extrapolated data from mitral regurgitation. This approach has limitations because the anatomy, hemodynamics, and regurgitant orifice geometry differ between the 2 valves (16).

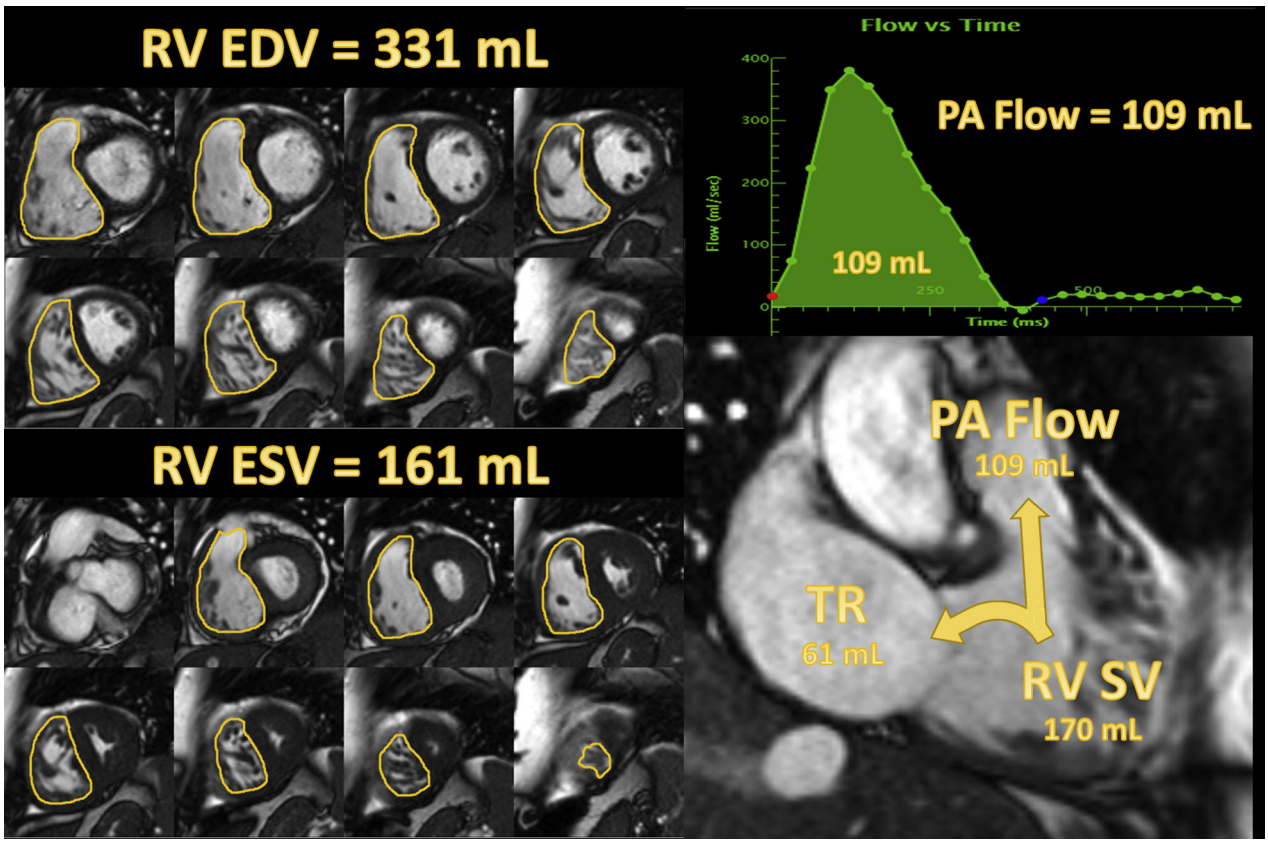
Current guidelines suggest using cardiovascular magnetic resonance (CMR) to evaluate right heart size and function in patients with severe TR (17) and assess reverse RV remodeling after tricuspid valve interventions (18). However, CMR can also quantify TR volume (TRVol) and TR fraction (TRF). CMR-quantified mitral and aortic regurgitant volume/fraction have shown to be strong adverse predictors in their respective left-sided valve lesions (19,20). To date, there has been no study evaluating the natural history of CMR-quantified measures of TR. Therefore, we investigated whether quantitative severity of functional TR remained an independent marker of mortality after adjustment for clinical and imaging covariates, including quantitative measures of RV ejection fraction (RVEF). In addition, we determined specific TR thresholds that would help identify a high-risk stratum of patients.

FIGURE 1 Flow Chart for Patient Selection



Of the 902 patients in our CMR registry with TR, a total of 355 patients were excluded from our analysis due to primary TR, confounding causes of RV remodeling, medical conditions with competing risk, and clinical or physiological factors that could affect TR quantitation. Our analysis focused on the remaining 547 patients. CMR = cardiovascular magnetic resonance; ICD = implantable cardioverter-defibrillator; PR = pulmonic regurgitation; RV = right ventricular; TR = tricuspid regurgitation.

FIGURE 2 **Assessment of TR Using CMR**



To calculate TR using CMR, RV SV is first calculated via the difference between RV end-diastolic and end-systolic volumes **(left panels)**. PA forward flow is then computed by using phase-contrast imaging to generate a flow curve **(top right)**. TR is calculated as the difference between RV SV and PA forward flow **(bottom right)**. In this example, TR is calculated at 61 ml. EDV = end-diastolic volume; ESV = end-systolic volume; PA = pulmonary artery; SV = stroke volume; other abbreviations as in Figure 1.

METHODS

PATIENT SELECTION. Consecutive patients undergoing CMR at the Houston Methodist Hospital (Houston, Texas) from 2008 through 2017 with findings of TR were enrolled into a prospective observational registry. We performed a thorough review of medical records at the time of imaging. Patients were excluded if they had primary tricuspid valve disease, confounding causes of RV remodeling (arrhythmogenic RV cardiomyopathy, congenital heart disease with shunting, or greater than mild pulmonary regurgitation), competing risk of noncardiac mortality from active malignancy, or factors that could affect optimal image quality such as implanted pacemaker/defibrillators.

Patients in atrial fibrillation at the time of imaging were excluded because of inherent beat-to-beat variability in the quantity of TR. However, patients with history of atrial fibrillation who were in sinus rhythm at the time of imaging were included in the final cohort. After exclusions, there were a total of 547 patients (Figure 1). The Institutional Review Board of the Houston Methodist Research Institute approved the study, and patients provided written informed consent.

CLINICAL ASSESSMENT. In addition to baseline medical history, cardiac risk factors, heart failure symptoms, and current medication use, an extensive medical record review was conducted to compile a Charlson Comorbidity Index. Invasive hemodynamic or echocardiography data, if performed within 6 months of the CMR examination and without any interim cardiac intervention, were analyzed to determine systolic pulmonary pressures and left ventricular (LV) filling pressures (see the "Evaluation of Pulmonary Pressures and LV Filling Pressures"

TABLE 1 Baseline Characteristics and Univariate Parameters Associated With Mortality

	All Patients (N = 547)	Alive (n = 454)	Dead (n = 93)	HR (95% CI)	p Value
Clinical characteristics					
Age, yrs	60 (49–69)	59 (47–68)	65 (56–73)	1.03 (1.01–1.04)	0.001
Male	292 (53)	241 (53)	51 (55)	1.18 (0.79–1.79)	0.42
Race/ethnicity					
White	355 (65)	302 (67)	53 (57)	(reference)	—
African American	125 (23)	92 (20)	33 (36)	1.78 (1.15–2.76)	0.01
Hispanic	47 (9)	42 (9)	5 (5)	0.72 (0.29–1.79)	0.48
Asian	14 (3)	12 (3)	2 (2)	0.90 (0.22–3.69)	0.88
Other	6 (1)	6 (1)	0 (0)	NA	NA
Body mass index, kg/m^2	27 (24–31)	27 (24–31)	26 (22–31)	0.97 (0.93–1.00)	0.07
GFR, ml/min/1.73 m^2	75 (57–93)	76 (61–93)	64 (44–86)	0.99 (0.98–1.00)	0.02
Hypertension	336 (61)	270 (60)	66 (71)	1.47 (0.94–2.30)	0.09
Diabetes	117 (21)	87 (19)	30 (32)	1.84 (1.19–2.84)	0.01
Smoking	200 (37)	157 (35)	43 (46)	1.47 (0.97–2.20)	0.07
Paroxysmal atrial fibrillation	114 (21)	94 (21)	20 (22)	1.04 (0.64–1.71)	0.86
Coronary artery disease	120 (22)	87 (19)	33 (36)	1.91 (1.25–2.92)	0.003
Prior myocardial infarction	77 (14)	60 (13)	17 (18)	1.28 (0.76–2.17)	0.36
Chronic lung disease	22 (4)	9 (2)	12 (13)	4.50 (2.45–8.28)	<0.001
Endocarditis	3 (1)	3 (1)	0 (0)	—	—
New York Heart Association					
Functional class					
Class I	204 (37)	182 (40)	22 (24)	(reference)	—
Class II	251 (46)	202 (45)	49 (53)	1.75 (1.06–2.89)	0.03
Class III	80 (15)	64 (14)	16 (17)	1.92 (1.01–3.66)	0.05
Class IV	12 (2)	6 (1)	6 (7)	5.41 (2.19–13.35)	0.001
Charlson Comorbidity Index	2 (1–4)	2 (1–3)	3 (2–5)	1.35 (1.21–1.51)	<0.001
Medications					
ACE inhibitor or ARB	222 (41)	192 (42)	30 (32)	0.66 (0.43–1.02)	0.06
Beta-blocker	292 (53)	239 (53)	53 (57)	1.12 (0.74–1.68)	0.60
Spironolactone	78 (14)	67 (15)	11 (12)	0.85 (0.45–1.59)	0.60
Nitrate	47 (9)	37 (8)	10 (11)	1.18 (0.61–2.28)	0.62
Diuretic	262 (48)	206 (45)	56 (60)	1.60 (1.06–2.43)	0.03
Digoxin	60 (11)	48 (11)	12 (13)	1.23 (0.67–2.25)	0.51
Acetylsalicylic acid	224 (41)	187 (41)	37 (40)	0.93 (0.61–1.41)	0.72
Imaging characteristics					
Left ventricular end-diastolic volume index, ml/m^2	87 (68–120)	88 (68–120)	82 (63–111)	1.00 (0.99–1.00)	0.14
Left ventricular end-systolic volume index, ml/m^2	36 (22–61)	36 (22–59)	36 (21–67)	1.00 (0.99–1.01)	0.90
Left ventricular end-myocardial mass index, g/m^2	73 (57–94)	72 (56–94)	76 (64–94)	1.00 (1.00–1.01)	0.49
Left ventricular ejection fraction, %	59 (41–70)	60 (43–70)	55 (38–68)	0.99 (0.98–1.00)	0.1
Cardiac index, l/min/m^2	2.4 (1.9–2.9)	2.4 (1.9–2.9)	2.2 (1.7–2.7)	0.79 (0.61–1.03)	0.09
Myocardial scar size, % of left ventricle	0 (0–4)	0 (0–3)	2 (0–8)	1.03 (1.01–1.05)	0.001
Left atrial volume index, ml/m^2	60 (45–79)	61 (45–79)	59 (44–83)	1.00 (0.99–1.01)	0.97
Right ventricular end-diastolic volume index, ml/m^2	94 (78–121)	92 (77–119)	107 (86–126)	1.01 (1.00–1.01)	<0.001
Right ventricular end-systolic volume index, ml/m^2	46 (33–68)	44 (32–66)	57 (42–84)	1.01 (1.01–1.01)	<0.001
Right ventricular ejection fraction, %	51 (40–59)	52 (42–59)	45 (31–55)	0.97 (0.96–0.99)	<0.001
Tricuspid annulus diameter, mm	35 (31–40)	35 (31–40)	38 (32–42)	1.04 (1.01–1.07)	0.02
Right atrial volume index, ml/m^2	49 (36–70)	47 (35–66)	58 (42–83)	1.01 (1.00–1.01)	<0.001
Systolic pulmonary artery pressure,* mm Hg	44 (35–57)	43 (35–53)	51 (40–66)	1.02 (1.01–1.03)	<0.001
≥ Moderate-severe mitral regurgitation	77 (14.1)	65 (14.3)	12 (12.9)	0.91 (0.50–1.57)	0.76

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section in the Supplemental Appendix). The predominant underlying etiology of functional TR was classified using a hierarchical scheme as either from left heart disease (secondary to valvulopathy or myocardial disease), pulmonary hypertension, and isolated TR (see the "Classification of Tricuspid Regurgitation Etiology" section in the Supplemental Appendix).

TABLE 1 Continued

	All Patients (N = 547)	Alive (n = 454)	Dead (n = 93)	HR (95% CI)	p Value
Tricuspid regurgitation quantification					
TRVol, ml	20 (12–33)	19 (12–30)	24 (15–44)	1.02 (1.01–1.03)	0.001
TRVol, ml, per 10-ml increment	–	–	–	1.17 (1.07–1.28)	<0.001
TRVol, ml					
<30	384 (70)	331 (73)	53 (57)	(reference)	–
30–44	88 (16)	70 (15)	18 (19)	1.47 (0.86–2.51)	0.16
≥45	75 (14)	53 (12)	22 (24)	2.27 (1.38–3.76)	0.001
TRF, %	25 (16–38)	24 (15, -35)	34 (20–48)	1.40 (1.21–1.56)	<0.001
TRF, %, per 10% increment	–	–	–	1.39 (1.22–1.51)	<0.001
TRF, %					
<30	325 (59)	287 (63)	38 (41)	(reference)	
30–49	166 (30)	132 (29)	34 (37)	1.76 (1.10–2.80)	0.02
≥50	56 (10)	35 (8)	21 (23)	4.21 (2.46–7.19)	<0.001

Values are median (interquartile range) or n (%), unless otherwise indicated. *Available in 348 (64%) of patients.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; NA = not applicable; TRF = tricuspid regurgitant fraction; TRVol = tricuspid regurgitant volume.

CMR. CMR image acquisition. CMR images were acquired using 1.5- or 3.0-T clinical scanners (Siemens Avanto, Aera, and Skyra, Siemens Healthineers, Erlangen, Germany) with phased-array coil systems. Anatomic and functional assessment of the RV was performed on short-axis, 4-chamber, and RV inflow-outflow views using steady-state free-precession sequences (flip: 65° to 85°; repetition time: 3.0 ms; echo time: 1.3 ms; in-plane spatial resolution: 1.7 to 2.0 × 1.4 to 1.6 mm; thickness: 6 mm with a 4-mm gap; temporal resolution: 35 to 40 ms). Flow across the pulmonic and aortic valve was assessed using phase-contrast imaging (flip: 25° to 30°; repetition time: ~5 ms; echo time: 2.4 ms; in-plane spatial resolution: ~2.0 × 2.4 mm, thickness: 6 mm; and temporal resolution: ~40 to 50 ms).

CMR image analysis. RV volumes were calculated by summing the volumes from a stack of short-axis slices covering both ventricles from base to apex at the timepoints of end diastole and end systole and with colocalization from long-axis slices (Figure 2). This method has similar reproducibility as volumes calculated by using axial slices (21). The RV stroke volume (SV) was determined by subtracting the end-systolic volume from the end-diastolic volume. The RVEF was calculated by dividing the SV by the RV end-diastolic volume. Pulmonary artery (PA) flow, acquired at the level of the main PA, was computed by planimetry of PA borders on phase contrast to determine the flow and then integrating these flows to cover the entire cardiac cycle (22). To ensure accurate PA flow, this value was cross-validated with computed net aortic flow.

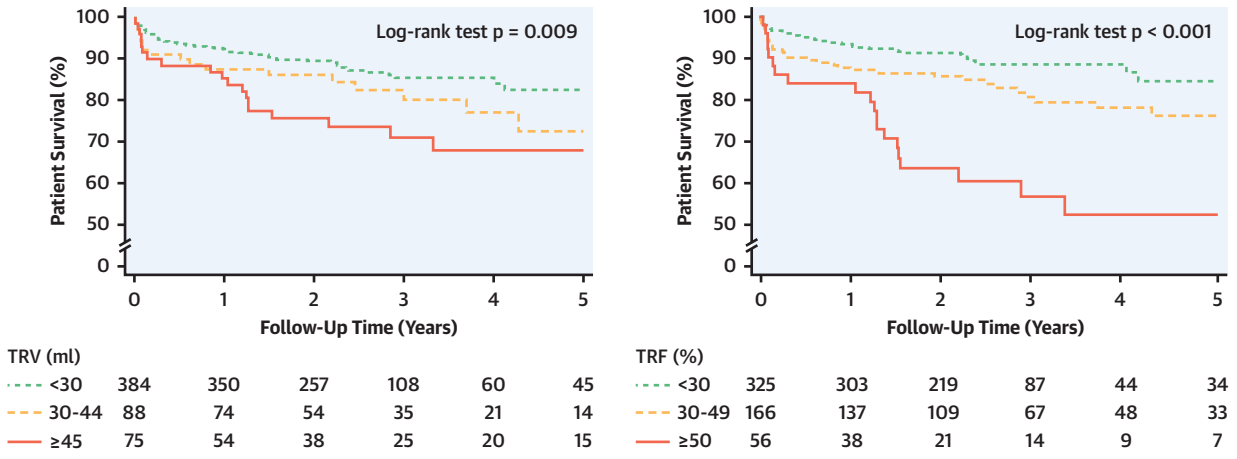
TRVol was calculated by subtracting PA forward flow, measured via phase-contrast imaging, from RV SV (Figure 2). TRF was calculated by dividing the TRVol by the RV inflow, which, in the absence of pulmonary regurgitation, is the RV SV. Interrater and intrarater reproducibility of TRVol and TRF were conducted on 15 randomly selected cases with a range of TR severities.

Other CMR variables. LV volumes, mass, and EF were measured as per recommended guidelines (22). LV fibrosis was assessed in a semiquantitative fashion, as previously described (23). Left atrial (LA) and right atrial (RA) volumes were measured by using the biplane area length and single-plane area length methods, respectively. The tricuspid annular diameter was measured in the 4-chamber view during the early diastolic cardiac phase (24).

OUTCOMES. Prospective follow-up of patients was conducted annually through structured phone interviews (patients and/or their family members), review of electronic health records, and/or contact with the referring clinic through December 6, 2018. The primary outcome was all-cause mortality. Patients who underwent tricuspid valve intervention or heart transplantation were censored at that time from further follow-up.

STATISTICAL ANALYSIS. Descriptive data are reported as frequencies and proportions for categorical variables and as either mean (95% confidence interval) or median (interquartile range [IQR]) for continuous variables. The chi-square or Fisher exact tests were used to compare differences in categorical variables, and the Kruskal-Wallis was used test for continuous variables. The optimal thresholds of TRF and TRVol in discriminating mortality risk were determined by the receiver-operating characteristic

FIGURE 3 Kaplan-Meier Estimates of Mortality According to TRVol and TRF



Kaplan-Meier estimates of mortality according to TRVol **(left)** and TRF **(right)**. Thresholds for mild **(green)** (TRVol of ≤30 ml or TRF of ≤30%), moderate **(yellow)** (TRVol of 30 to 44 ml or TRF of 30% to 49%), and severe **(red)** TR (TRVol of ≥45 ml and TRF of ≥50%) are displayed. TR = tricuspid regurgitation; TRF = tricuspid regurgitant fraction; TRVol = tricuspid regurgitant volume.

curve analysis with a Youden index (25). Multiple pairs of thresholds that differentiate patients with low risk versus moderate risk and moderate risk versus high risk were evaluated. The optimal pair of cutpoints was defined when the Youden index was maximized in all possible pairs as described by Luo et al. (26) on the extension of the Youden index to assess diagnostic accuracy when there are 3 ordinal diagnostic groups. Interrater and intrarater reliabilities were assessed using the intraclass correlation coefficient.

Patient survival was depicted by the Kaplan-Meier curves. Differences between groups were compared using the log-rank test. Cox proportional hazards modeling was used to determine the characteristics associated with mortality. Five different models were created. For models 1 through 4, covariates included in the multivariable models were decided by the clinicians based on the established risk factors described in the literature and based on clinical experience. To evaluate the added value of different types of covariates in discriminating the outcomes, covariates were added sequentially, such as age (model 1), Charlson Comorbidity Index (model 2), Charlson Comorbidity Index and left-sided imaging (model 3), and Charlson Comorbidity Index and biventricular imaging (model 4). For model 5 (statistical model), in order to not miss any potential risk factors, all variables evaluated in the univariable analysis were initially considered as potential candidates for the initial multivariable models by using the Bayesian model averaging (BMA) method. The discrimination power of the predicting models was assessed using the C-statistic. The best model was chosen based on the smallest Bayesian information criterion and largest C-statistic. When there was an inconsistency between the C-statistic and the Bayesian information criterion, models with a larger C-statistic were selected. All analyses were performed on Stata, version 16.1 (Stata Corp LLC, College Station, Texas). A p value of <0.05 was considered statistically significant. Adjusted spline models depicting the relationship between TRVol/TRF and mortality were also created.

RESULTS

BASELINE CHARACTERISTICS. Patients were median age of 60 years, with an equal proportion of men and women and ethnicities generally reflective of the U.S. population (27) (**Table 1**). The most common indication for CMR was cardiomyopathy (44%), followed by valvular heart disease assessment (41%), pulmonary hypertension (5%), and miscellaneous (10%). Aside from a history of hypertension, most patients did not have any other cardiovascular risk factors. The majority of patients were of NYHA functional class I or II. About one-half of the cohort reported taking heart failure medications.

Most patients had normal LV volumes, systolic function, mass, and cardiac index. The median extent of LV myocardial scar was 0% (IQR: 0% to 4%). The

TABLE 2 Successive Multivariable Cox Proportional Hazards Models Evaluating TRVol and TRF

	Univariate		Age		Clinical*		Clinical and Left-Sided Imaging†		Clinical and Biventricular Imaging‡		Statistical Model§	
	HR	p Value	AHR	p Value	AHR	p Value	AHR	p Value	AHR	p Value	AHR	p Value
TRVol, per 10 ml	1.17	0.001	1.14	0.002	1.12	0.01	1.17	0.001	1.15	0.004	1.10	0.051
TRVol, ml												
<30	(ref)	–	(ref)	–	(ref)	–	(ref)	–	(ref)	–	(ref)	–
30–44	1.47	0.16	1.43	0.19	1.47	0.16	1.57	0.10	1.46	0.12	1.32	0.32
≥45	2.27	0.001	2.34	0.001	2.08	0.004	2.39	0.001	2.26	0.002	1.70	0.04
TRF, per 10%	1.37	<0.001	1.34	<0.001	1.31	<0.001	1.34	<0.001	1.26	0.001	1.21	0.01
TRF, %												
<30	(ref)	–	(ref)	–	(ref)	–	(ref)	–	(ref)	–	(ref)	–
30–49	1.70	0.03	1.58	0.06	1.49	0.09	1.51	0.09	1.21	0.45	1.12	0.66
≥50	3.90	<0.001	3.75	<0.001	3.17	<0.001	3.52	<0.001	2.60	0.001	2.42	0.003

*Adjusted for Charlson Comorbidity Index. †Adjusted for Charlson Comorbidity Index, left ventricular ejection fraction, left atrial volume index, and mitral regurgitation severity. ‡Adjusted for Charlson Comorbidity Index, left ventricular ejection fraction, left atrial volume index, mitral regurgitation severity, and right ventricular ejection fraction. §Adjusted for sex, race, Charlson Comorbidity Index, right ventricular ejection fraction, and ACE inhibitor/ARB use.

AHR = adjusted hazard ratio; ref = reference; other abbreviations as in Table 1.

median LA volume index was mildly increased at 60 ml/m^2 (IQR: 45 to 79 ml/m^2) (28). Most patients had normal RV end-diastolic and end-systolic volumes, tricuspid annulus diameters, and RA volumes. RV function was depressed, with a median of RVEF 51% (IQR: 40% to 59%) (lower limits by CMR is 56%) (29). Median systolic pulmonary pressures were elevated at 44 mm Hg (IQR: 35 to 57 mm Hg). PA pressures were available by invasive hemodynamics or echocardiography in 368 (67%) patients.

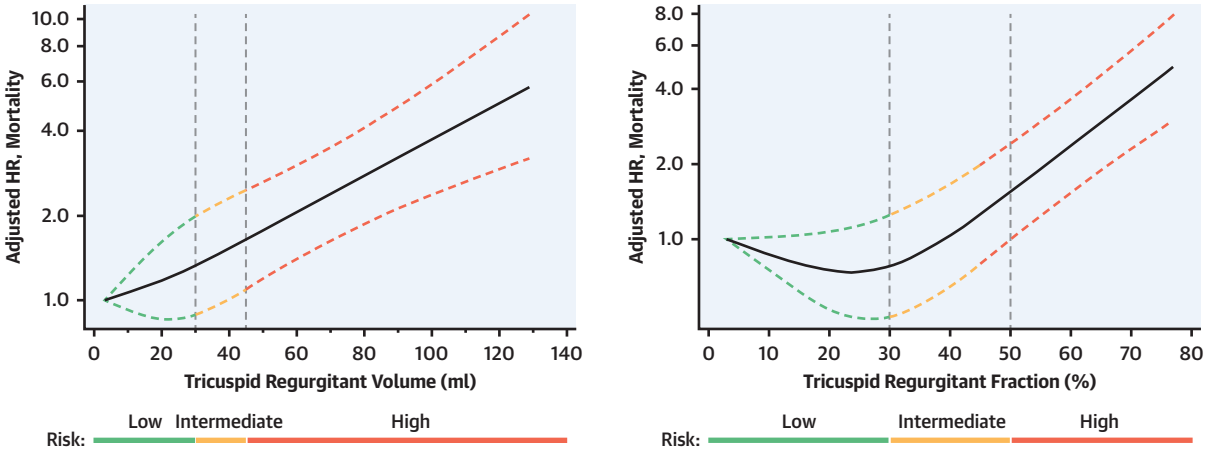
The median TRVol and TRF were 20 ml (IQR: 12 to 33 ml) and 25% (IQR: 16% to 39%), respectively. The etiology of secondary TR was attributed to left-sided valvular disease (43%), myocardial disease (33%), isolated causes (18%), and pulmonary hypertension (6%). Intrarater and inter-rater reproducibility of TR was good, with an intraclass correlation coefficients of 0.97 and 0.83, respectively. A full description of the baseline characteristics stratified by etiology of TR (Supplemental Table 1) and TR reproducibility results (see the "Intrarater and Interrater Reproducibility of TRVol and TRF" section) are in the Supplemental Appendix.

FOLLOW-UP AND SURVIVAL. Patients were followed up 9.3 years (median: 2.6 years; IQR: 1.7 to 3.3 years). During follow-up, 93 (17%) patients died, 63 (12%) underwent left-sided valve surgery, 13 (2.3%) underwent tricuspid valve surgery, and 11 (2%) underwent heart transplant. Of the 13 patients who underwent TV surgery, 2 (0.4%) underwent surgery for isolated TR, and 6 (1.1%) underwent surgery for severe TR at time of mitral or aortic intervention. An additional 5 (0.9%) patients underwent TV surgery at the time of left-sided surgery and had a dilated TV annulus, with the TRVol in these patients ranging from 12 to 48 ml and the TRF ranging from 27% to 47%. The annualized death rate for the entire cohort was 5.9%, with overall 1-, 3-, and 5-year survivals of 91%, 83%, and 79%, respectively.

Univariate analysis (Table 1) showed multiple clinical variables associated with increased mortality: age, African-American race, glomerular filtration rate, diabetes, coronary artery disease, presence of dyspnea, increasing NYHA functional class, increasing diuretic use, and a higher Charlson Comorbidity Index. Among the left heart imaging variables, only LV myocardial scar burden was associated with increased risk of death. LV volumes and function were not different between patients who survived and died. Conversely, numerous right heart parameters, such as larger RV end-diastolic volume index, larger RV end-systolic volume index, lower RVEF, increased tricuspid annulus diameter, increased RA volume index, and higher systolic PA pressure, were associated with mortality (Table 1).

The quantitative severity of TR, by both volume and fraction, was associated with death, with a univariate hazard ratio of 1.17 (95% confidence interval [CI]: 1.07 to 1.27; $p = 0.001$) for every 10 ml of TRVol and 1.37 (95% CI: 1.21 to 1.55; $p < 0.001$) for every 10% of TRF. Using survival receiver-operating characteristic analysis, TRVol of <30 ml, 30 to 44 ml, and ≥45 ml identified the low, intermediate, and high-risk strata, respectively (Figure 3). Similarly, a TRF of <30%, 30% to 49%, and ≥50% identified optimal thresholds for low, intermediate, and

FIGURE 4 Adjusted Spline Models Depicting the Effect of Tricuspid Regurgitant Volume and Fraction



Dashed lines depict 68% confidence intervals. Adjusted for Charlson Comorbidity Index, left ventricular ejection fraction, left atrial volume index, and right ventricular ejection fraction. TRF = tricuspid regurgitant fraction; TRV = tricuspid regurgitant volume.

high-risk strata, respectively (Figure 3). Patients in the highest TRVol (≥45 ml) and TRF (≥50%) strata had 1-year mortalities of 15% and 14%, respectively.

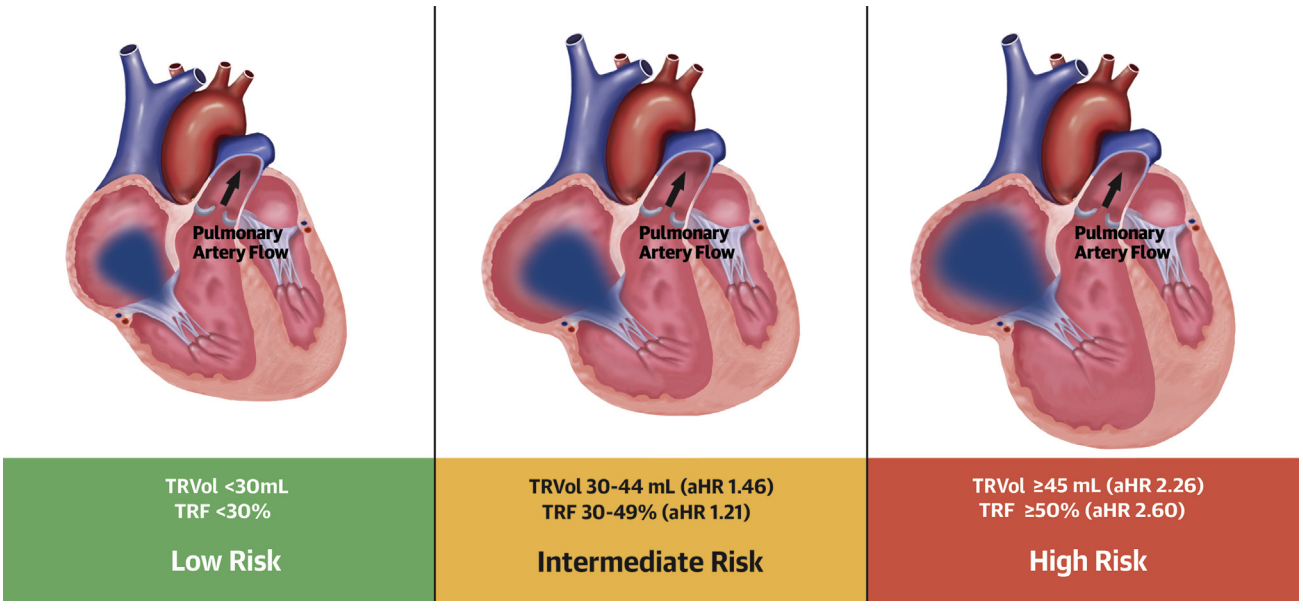
MULTIVARIABLE SERIAL ANALYSIS OF FUNCTIONAL TR AND SURVIVAL. Pairwise comparison between different clinically selected multivariable Cox proportional hazard models showed that TRVol, as a continuous variable, was associated with mortality (Table 2). In these models, TRVol remained significant despite serial progressive adjustments for age, Charlson Comorbidity Index, LA volume, LVEF, mitral regurgitation severity, and RVEF. When accounting for clinical and biventricular imaging variables, a 10-ml increase in TRVol was associated with an adjusted hazard ratio (AHR) of 1.15 (95% CI: 1.04 to 1.26) for death. Using variables selected through a BMA method, TRVol showed a strong trend for mortality, with an AHR of 1.1 (95% CI: 1.0 to 1.2; p = 0.051) after adjustment for Charlson Comorbidity Index, RVEF, sex, race, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. When analyzing TRVol by stratum, the highest group with TRVol of ≥45 ml was associated with increased mortality in all clinical and BMA models compared to the lowest-risk stratum of TRVol of <30 ml, with an AHR of 2.26 and 1.7, respectively.

Pairwise comparison between different clinically selected multivariable Cox proportional hazard models demonstrated that TRF, as a continuous variable, was associated with adverse mortality (Table 2) in all clinical models and the BMA method. When accounting for clinical and biventricular imaging variables, a 10% increase in TRF was associated with an AHR of 1.26 (95% CI: 1.1 to 1.45) for death. Using variables selected through a BMA method, TRF had a similar AHR of 1.21 (95% CI: 1.05 to 1.40) of death. When analyzing TRF by stratum, using the 3 strata of severity, the highest-risk group with TRF ≥50% has an increased mortality in all clinical and BMA models compared to the lowest-risk stratum of TRVol <30%, with an AHR of 2.60 and 2.42, respectively. Adjusted cubic spline curves depict the relative linear increase in mortality with TRVol but a J-shaped increase in mortality with TRF (Figure 4). Full models exploring the impact of the adjusted variables are available in the Supplemental Appendix (Supplemental Table 2). Because 67% of patients had available systolic PA pressures, a sensitivity analysis was performed to assess the impact of adjustment for this covariate. It demonstrated similar findings to our entire cohort (Supplemental Tables 3 and 4).

DISCUSSION

In our study of patients with functional TR, we explored the association of TRVol and TRF as potential predictors of all-cause mortality. Both parameters, when assessed as categorical variables, were associated with mortality on univariate and multivariate analyses, with distinct categories of low, intermediate, and high risk (Central Illustration). Similar findings were seen with analysis of TRVol and TRF as continuous variables, with the exception that TRVol demonstrated only a strong trend toward mortality after adjustment for BMA variables (p = 0.051).

CENTRAL ILLUSTRATION **3 Risk Categories for Functional Tricuspid Regurgitation Can Be Defined: Low, Intermediate, and High Risk**



Zhan, Y. et al. J Am Coll Cardiol. 2020;76(11):1291–301.

A tricuspid regurgitant volume (TRVol) of <30 ml or a tricuspid regurgitant fraction (TRF) of <30% is associated with the lowest risk **(left panel; green)**. Intermediate risk is classified as a TRVol of 30 to 44 ml or a TRF of 30% to 49% **(middle panel; yellow)**. The highest-risk group consists of patients with a TRVol of ≥45 ml or a TRF of ≥50% **(right panel; red)**. HR = hazard ratio.

The absolute mortality risk attributable to TR increased as either TRVol or TRF increased. We found that patients in the highest-risk strata of functional TR, TRVol ≥45 ml or TRF ≥50%, had a 2.3- and 2.6-fold increased risk of death, compared to the low-risk strata. These findings included adjustment for quantitative RVEF, a powerful confounder of mortality that was not adjusted for in any prior studies of TR. Additionally, we adjusted for the multiple comorbidities in these patients using the Charlson Comorbidity Index. RV volume was originally a candidate variable for adjustment, but it was colinear with TRVol and was less of a discriminator of mortality compared to RVEF, which is consistent with prior findings (30).

The fact that similar associations were found using clinical multivariate models and the statistical BMA method reflect the robust nature of the association of TRVol/TRF with mortality. The statistical BMA method has been shown to be superior to other methods in the context of variable selection in epidemiological studies, including datasets with Framingham Heart Study data and is likely to select true predictors of mortality and reduce redundant variable selection (31–33).

TRVol and TRF are related but not identical. Although both parameters incorporate the volume of regurgitation, only the regurgitant fraction considers the total volume of blood ejected by the ventricle and, therefore, adjusts for systemic flow. Functional TR, by its inherent nature, frequently occurs in a low-flow state, where a relatively small TRVol can yield a larger TRF. For example, the same regurgitant volume of 30 ml will yield a regurgitant fraction of 30% if the ventricle is ejecting 100 ml but would yield a regurgitant fraction of 50% if the ventricle is ejecting only 60 ml of blood with each cardiac cycle. This discrepancy may explain why echocardiographic studies quantitating TRVol, in the setting of patients with depressed LV function and probable low-flow states, have shown lower regurgitant volumes associated with increasing mortality (5,6). Similar findings have been reported in patients with low systemic flow states with functional mitral regurgitation (34). Therefore, in a population with varying flow states, TRVol may not be as robust as TRF in integrating the

underlying impact of TR on the ventricle and, ultimately, on mortality.

Interestingly, our outcomes-based risk strata for the degrees of TRVol were similar to findings in patients with secondary MR, where ≥45 ml or ≥50% of regurgitation portended the greatest excess mortality (35). This suggests that physiologically, the relative volume overload and clinical response of the RV may be analogous to that of the LV with secondary mitral regurgitation. Additionally, this reinforces the concept that valvular regurgitation becomes consequential when lost backward flow into the atrium exceeds the ventricular forward SV (34,35).

Outcomes were limited to all-cause mortality to investigate the natural history. Heart failure hospitalization was not evaluated to avoid potential misclassification bias that is not present with all-cause mortality. Additionally, a combined outcome of tricuspid valve surgery and death was not entertained because most surgeries for functional TR are performed only during left-sided valve surgery. In our cohort, only 2 of 13 tricuspid surgeries were performed without concomitant left-sided heart surgery. Therefore, a combined endpoint, which includes surgical intervention, may not reflect surgery due to severe TR. Additionally, data on cardiac death or heart failure hospitalization were not collected because of potential classification bias.

There is a paucity of guideline recommendations for intervention in the setting of severe TR because of limited data on natural history and surgical experience (17,36). In patients with moderate or severe TR, only 2% of patients ultimately receive isolated tricuspid valve surgery. Nationally, it is estimated that fewer than 800 tricuspid replacements or repairs are performed annually (12,37), with high in-hospital mortality approaching 9% (12). However, in our study, the mortality from functional TR at 1 year was 15% in those with a TRV of ≥45 ml and 14% in medically treated patients with a TRF ≥50%. Transcatheter tricuspid valve repair techniques have shown a lower mortality of 3.7% (13) and may be promising options for patients with severe TR at high surgical risk (38).

STUDY LIMITATIONS. Our study excluded several patient groups, such as those who were in atrial fibrillation at the time of imaging (consisting of 13% of our cohort). This was done because of the inherent beat-to-beat variability in the magnitude of TR. PA flow quantitation used interpolation-based offset correction, which has been shown to be as accurate as phantom-based offset correction (39). Additionally, the severity of TR is dynamic, and it can be affected by changes in pre-load (as occurs with diuresis). Therefore, our measurements of TRVol and TRF may not reflect the patient's usual severity of TR after effective heart failure management. Third, functional TR is a complex disease with many underlying causes, each with its own specific risk factors. Although we attempted to adjust for most of these risk factors, we likely could not account for all. An analysis of cardiac death or heart failure hospitalization was not made in our cohort because, unlike all-cause mortality, such analysis suffers from classification bias. Finally, insights regarding the implication of differing TR etiology with mortality could not be made because most patients in our cohort had TR secondary to left heart disease.

CONCLUSIONS

This is the first study to use CMR to study the natural history of TR. The quantified severity of functional TR was independently associated with excess mortality, even after adjustment for clinical and imaging confounders, including RVEF. A TRVol of ≥45 ml or TRF of ≥50% had the greatest risk for excess mortality under medical management, with an AHR of 2.3 and 2.6 compared to a TRVol of <30 ml or TRF of <30%, respectively. Future randomized controlled trials using these thresholds will determine if tricuspid valve intervention may benefit this high-risk group.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Functional TR as assessed by CMR imaging is an independent predictor of mortality, even after adjustment for clinical and ventricular variables including RVEF.

TRANSLATIONAL OUTLOOK: Further studies are needed to compare the clinical utility of quantifying TR by echocardiography or CMR as a predictor of clinical outcomes and the effect of therapeutic interventions.

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KEY WORDS cardiovascular magnetic resonance, natural history, prognosis, tricuspid regurgitation, tricuspid valve

APPENDIX For an expanded Methods section as well as supplemental tables, please see the online version of this paper.