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ORIGINAL RESEARCH

Quantitative Echocardiographic Assessment and Optimal Criteria for Early Intervention in Asymptomatic Tricuspid Regurgitation

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ABSTRACT

BACKGROUND Significant tricuspid regurgitation (TR) is associated with poor outcome and high operative mortality resulting from late presentation. Yet, the optimal timing for intervention is unknown.

OBJECTIVES The purpose of this study was to evaluate the prognostic value of echocardiographic parameters to inform early intervention in asymptomatic TR.

METHODS Using the Cleveland Clinic echocardiography database 2004 to 2018, the authors identified a consecutive cohort of asymptomatic patients with moderate to severe (3+) or severe (4+) TR. Quantitative TR and right heart parameters were retrospectively determined, and their prognostic utility for all-cause mortality was assessed.

RESULTS In 325 asymptomatic patients (mean age: 67.9 years; 79.4% female) with at least 3+ TR, there were 132 deaths (40.6%), with a median survival time of 9.9 years (95% CI: 7.9-12.7 years). By contrast, the median survival time in an age- and sex-matched cohort of symptomatic TR patients was 4.4 years (95% CI: 2.8-5.9 years). Among all the echocardiographic parameters evaluated, right ventricle free wall strain (RVFWS) and tricuspid regurgitant volume (RVol) were the strongest predictors of mortality in asymptomatic TR. The optimal discriminatory thresholds for these parameters were RVFWS $<-19\%$ and RVol >45 mL. The 5-year survival rates by number of risk factors (RF) were 93% (95% CI: 86%-96%), 65% (95% CI: 55%-74%), and 38% (95% CI: 26%-49%) for no RF, 1 RF, and both RFs, respectively. Compared with symptomatic TR, mortality was lower for asymptomatic TR with no RF (HR: 0.10; 95% CI: 0.04-0.29) or 1 RF (HR: 0.29; 95% CI: 0.14-0.58), but similar for asymptomatic TR with both RFs (HR: 1.11; 95% CI: 0.56-2.19).

CONCLUSIONS RVFWS and RVol are key prognostic markers that can be serially monitored to inform optimal timing of intervention for severe asymptomatic TR. (J Am Coll Cardiol Img 2023;16:13-24) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

EROA = effective regurgitant orifice area

LVEF = left ventricle ejection fraction

PISA = proximal isovelocity surface area

RVFWS = right ventricle free wall strain

RVGLS = right ventricle global longitudinal strain

RVol = tricuspid regurgitant volume

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

Severe tricuspid regurgitation (TR) is associated with adverse clinical outcomes in patients with or without symptoms.[1,2] Yet, it has been vastly undertreated.[3,4] The current American College of Cardiology/American Heart Association (ACC/AHA) valve guidelines only give a Class 1 recommendation for TR surgery if being performed concomitantly with left heart surgery.[5] Hence, it is not surprising that isolated TR surgery is rare and is often delayed until patients are too sick to undergo surgery.[6,7] This delay in surgery to the late stage of the disease when symptoms or right ventricular failure have developed contributes to its markedly higher surgical risk compared with other isolated valve operations.[8]

In recent years, there have been renewed interest and significant advances in imaging and therapeutic options for TR.[3,9] However, there remains a lack of data on predictors of disease progression and adverse outcome, particularly in lower-risk and asymptomatic patients with isolated TR, to inform optimal timing of intervention. These are important issues to address to improve outcomes in these patients. Given that the disease progression translates to structural remodeling in the right heart chambers, it is expected that such structural remodeling will predict subsequent clinical outcomes in these patients. Hence, the main objective of this study was to evaluate echocardiographic TR and right heart parameters that predict outcomes in asymptomatic TR patients with the aim of identifying the optimal criteria to inform early intervention. In addition, we evaluated the potential impact of delaying surgery until symptom onset by comparing echocardiographic parameters and clinical outcomes between asymptomatic and symptomatic TR patients.

METHODS

STUDY POPULATION. We retrospectively reviewed the Cleveland Clinic echocardiography database, which includes all echocardiograms performed within the Cleveland Clinic main campus and its affiliated hospitals. We included data on consecutive adult patients (≥18 years of age) who had moderate to severe (3+) or severe (4+) TR between January 2004 and December 2018. Follow-up data were accrued up until June 2021. We excluded patients with other significant valvular disease defined as at least moderate regurgitation or at least mild stenosis, prior heart transplantation, and congenital heart disease. We additionally excluded patients with TR caused by endocarditis, cardiac implantable electronic devices, prior tricuspid valve surgery, symptomatic atrial fibrillation, any sustained arrhythmia at the time of echocardiography, or prior heart failure hospitalization (**Figure 1**). Clinical data on the remaining patients were reviewed to identify symptom status within 6 months of the baseline echocardiography. Asymptomatic TR was defined as the absence of dyspnea, fatigue, ascites, peripheral edema, and other heart failure signs.[5] Ethics approval was attained from our Institutional Review Board (19-993) with a waiver of the requirement to obtain patient informed consent.

CLINICAL CHARACTERISTICS. Baseline clinical characteristics, including demographics, comorbidities, and laboratory results, were extracted from a detailed review of electronic health records. Asymptomatic TR status was individually adjudicated by a review of clinical documentation within 6 months of the baseline echocardiography, including but not limited to chief complaints, history of presenting illness, review of systems, past medical history, current medications, physical examination findings, and assessment and plan. Perioperative surgical risk was calculated based on the dedicated risk score models for isolated tricuspid valve surgery: TRI-SCORE and LaPar's Society of Thoracic Surgeons clinical risk score.[10,11]

ECHOCARDIOGRAPHY ASSESSMENT. Based on standard institutional protocol, echocardiography was performed with Vivid 7 or Vivid E9 (GE Healthcare) or EPIQ 7C (Philips Medical Systems) machines. The initial echocardiography reading was done by expert readers, and we retrospectively reviewed the images to ensure that they were consistent with current American Society of Echocardiography guidelines.[12] Measurements of TR parameters and chamber quantification were done with Syngo Dynamics (Siemens Medical Solutions). Briefly, for the assessment of TR, all tricuspid valve views with color Doppler were assessed for each patient, and the view with the largest and best-visualized proximal isovelocity surface area (PISA) shell was used for TR quantification. As recommended in the guidelines,[12] vena contracta width was measured as the narrowest part of the regurgitant jet; PISA radius (r) of the flow convergence was measured from the point of color Doppler aliasing to the vena contracta at a time in the cardiac cycle that coincided with the peak velocity of the jet; effective orifice area (EROA) was calculated as ($2\pi r^2 \times$ color Doppler aliasing velocity) divided by the peak velocity of the regurgitant jet as determined by continuous wave Doppler; and regurgitant volume (RVol) as the product of EROA and the velocity time

integral of the jet. Chamber quantification, including dimension and function analysis, was performed as recommended in the guidelines,[13] and areas and volumes were indexed to the body surface area. Last, strain analysis was done by velocity vector imaging (Siemens Medical Solutions), which is a vendor-independent software that uses a speckle-tracking technology for strain analysis. As recommended,[14] the right ventricle free wall longitudinal strain (RVFWS) was calculated as average strain over the 3 lateral wall segments, and right ventricle global longitudinal strain (RVGLS) was averaged over the 3 lateral walls and 3 septal walls.

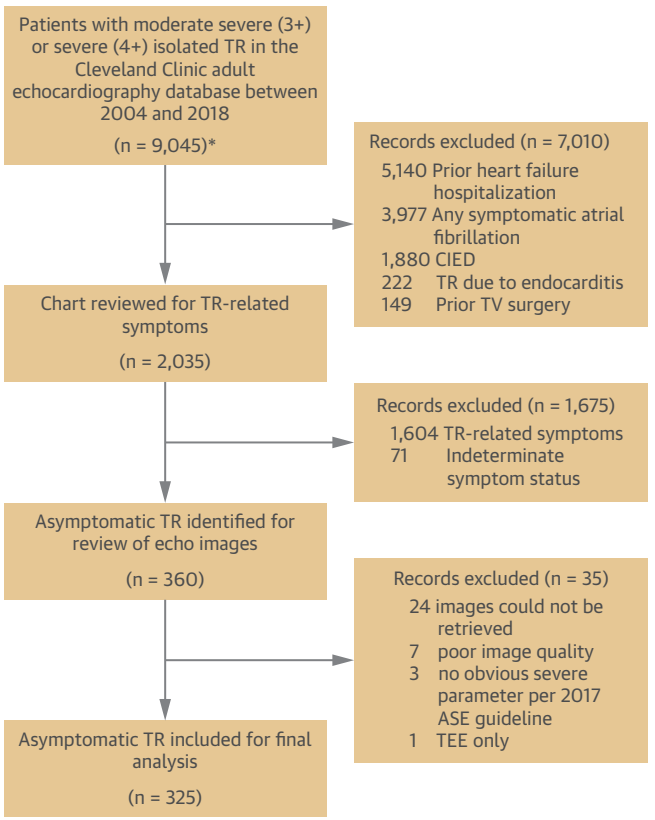
B-TYPE NATRIURETIC PEPTIDE. To evaluate the correlation between the echocardiographic parameters and biomarkers of myocardial stress, namely, B-type natriuretic peptide (BNP), we extracted data on BNP values determined within 6 months of the echocardiogram. All samples were measured by the Cleveland Clinic main laboratory under standard institutional protocol. Briefly, BNP was measured from EDTA plasma samples using direct chemiluminescent technology of the ADVIA Centaur BNP assay (Siemens Healthcare). This assay detects BNP in the range of <2.0 pg/mL to 5,000 pg/mL with coefficient of variation <5%.[15]

OUTCOMES. The primary endpoint for the analysis was all-cause mortality. Death was individually adjudicated through a search of clinical health records, state mortality databases, and obituaries up to June 2021. The follow-up time was from the time of baseline echocardiography to the time of death or, for those still alive, the last known hospital contact.

STATISTICAL ANALYSIS. The baseline characteristics and echocardiographic parameters of the cohort of interest with asymptomatic TR were compared with an age- and sex- matched cohort of patients with symptomatic TR and preserved LVEF using a paired Student's *t*-test or Wilcoxon signed-rank test (as appropriate) for continuous variables and the McNemer test for categorical variables. Intraobserver and interobserver agreement in the PISA-derived measurements and strain were assessed by Pearson correlation coefficient and Bland-Altman analysis. The potential implication of symptom onset was evaluated by comparing the mortality outcomes in patients with asymptomatic TR with those of the age- and sex-matched cohort with symptomatic TR using the Cox proportional hazard model stratified on the matching pairs. Only symptomatic patients with preserved LVEF were considered for the analysis to limit the confounding effect of left ventricular dysfunction. In addition, for the Cox model analysis comparing mortality between the 2 cohorts, we adjusted for baseline covariates that were significantly different between the 2 matched cohorts (Table 1).

The prognostic value of the echocardiographic parameters to inform timing for early intervention among patients with asymptomatic TR was evaluated in 3 steps. First, in a subset of the patients who had BNP levels within 6 months of the echocardiography, we evaluated the correlation between each parameter and BNP, a biochemical marker of myocardial stress. The BNP values were log-transformed to account for their skewed distribution, and the strength of correlation was assessed by the Pearson correlation coefficient (r). Second, we assessed the association between each echocardiographic parameter and all-cause mortality (in separate models) using a multivariable-adjusted Cox model (ie, Model 1_i, where $_i$ represents each model). Each model adjusted

FIGURE 1 Sample Selection Algorithm



*This number represents initial screening after exclusion of other significant valvular disease defined as at least moderate regurgitation or at least mild stenosis, prior heart transplantation, and congenital heart disease. ASE = American Society of Echocardiography; CIED = cardiac implantable electronic device; TEE = transesophageal echocardiogram; TR = tricuspid regurgitation; TV = tricuspid valve.

TABLE 1 Baseline Clinical Characteristics of Asymptomatic TR Patients Compared With Age- and Gender-Matched Patients With Symptomatic TR

	Asymptomatic (n = 325)	Symptomatic (n = 325)	*P* Value
Age, y	67.9 ± 16.9	67.9 ± 16.9	1.00
Female	258 (79.4)	258 (79.4)	1.00
Race			0.63
White	236 (72.6)	241 (74.1)	
Black	80 (24.6)	75 (23.1)	
Asian	4 (1.2)	3 (0.9)	
Other	5 (1.5)	6 (1.9)	
Body surface area, m^2	1.7 ± 0.25	1.8 ± 0.27	<0.001
Body mass index, kg/m^2	26.8 ± 7.4	29.2 ± 8.8	<0.001
Hypertension	168 (51.6)	215 (66.1)	<0.001
Diabetes	38 (11.6)	85 (26.1)	<0.001
Smoking history	138 (42.4)	162 (49.8)	0.070
Prior myocardial infarction	10 (3.1)	29 (8.9)	0.005
Prior stroke	25 (7.6)	36 (11.1)	0.180
Peripheral vascular disease	20 (6.1)	43 (13.2)	0.001
Prior cardiac surgery			
Any cardiac surgery	63 (19.3)	95 (29.2)	0.005
Left valve surgery	17 (5.2)	47 (14.4)	<0.001
CABG	39 (12.0)	40 (12.3)	0.990
Chronic lung disease	65 (20)	114 (35)	<0.001
Primary tricuspid regurgitation	21 (6.5)	13 (4.0)	0.210
Laboratory values[a]			
BNP, pg/mL	123 (50-463)	286 (153-715)	NR
Creatinine, mg/dL	0.91 (0.75-1.20)	1.21 (0.88-1.70)	<0.001
GFR, mL/min/1.73 m^2	68.4 (49.8-85.4)	50.5 (34.0-69.0)	<0.001
Bilirubin, mg/dL	0.50 (0.30-0.70)	0.65 (0.40-1.20)	NR
Medication			
Loop diuretic	0 (0)	218 (67.1)	<0.001
ACEI/ARB	31 (9.5)	64 (19.7)	<0.001
Beta-blocker	47 (14.5)	172 (52.9)	<0.001
Mineralocorticoid	2 (0.62)	42 (12.9)	<0.001
Perioperative surgical risk			
TRI-SCORE	1 (1-2)	4 (3-5)	<0.001
LaPar STS clinical risk score	3 (1-4)	6 (4-7)	<0.001
TV surgery during follow-up	9 (2.8)	45 (13.9)	<0.001

Values are mean ± SD, n (%), or median (IQR). [a]Only laboratory values within 6 months of the echocardiography were extracted. BNP was available in 95 asymptomatic, 200 symptomatic patients. Bilirubin was available in 54 asymptomatic, 150 symptomatic patients.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; GFR = glomerular filtration rate; NR = not reported (ie, *P* value not reported because of small number of matched pairs with laboratory values within 6 months); STS = Society of Thoracic Surgeons; TR = tricuspid regurgitation; TRI-SCORE = risk score for in-hospital mortality prediction after isolated tricuspid valve surgery; TV = tricuspid valve.

for potential confounding variables that were determined a priori based on the review of current literature on TR and understanding of their effect on mortality, namely age, sex, race, prior cardiac surgery, cause of TR (primary if leaflet pathologic changes are evident vs functional if otherwise), TR surgery during follow-up, glomerular filtration rate, LVEF, diabetes, hypertension, and prior vascular event (ie, any of myocardial infarction, stroke, or peripheral vascular disease). Third, to identify the best predictors of mortality among all the echocardiographic parameters, we used a backward stepwise selection procedure (P exclusion = 0.20; P inclusion = 0.10) to select from echocardiographic parameters that were significant from Model 1_i. This stepwise selection model was adjusted for the same covariates as specified above for Model 1_i. Multicollinearity was assessed by variance inflation factor, and those with values >10 were excluded from the final selection model. Proportionality assumption was assessed by scaled Schoenfeld residuals, and an interaction term with time was introduced for the variable that failed the proportionality test. Echocardiographic parameters that remained significant in the stepwise selection model were considered the best parameters for predicting mortality, and their optimal discriminatory threshold for predicting 5-year mortality was determined by the Youden index, which maximizes the sum of sensitivity and specificity.[16,17] Data were complete on all variables with few missing values, including RV strain in 9.5% caused by limited visualization of the free wall, right atrial strain in 5.5%, and tricuspid annular plane systolic excursion (TAPSE) in 4.5% (Supplemental Table 1). In 3 studies, PISA and PISA-related measurements were not possible because of poor visualization of the flow convergence. For each of these variables with missing values, we performed multiple imputations using the data augmentation algorithm of the Markov Chain Monte Carlo procedure. Ten imputations were performed for each missing value, and estimates were pooled over the imputed data sets for the main analyses, including prediction model, selection model, and Youden index. Variables with >40% missing values (tricuspid annular systolic velocity and estimated right atrial pressure) were not considered for imputation or in the selection model. To evaluate the robustness of our result, we also performed complete case analysis involving only patients with nonmissing values as a sensitivity analysis.

All analysis was performed using STATA 17 (StataCorp), and a 2-tailed value of $P < 0.05$ was considered statistically significant.

RESULTS

From a cohort of 9,045 patients with moderate to severe (3+) or severe (4+) TR who were seen in the Cleveland Clinic between 2004 and 2018, we identified 325 consecutive patients with asymptomatic TR (Figure 1). The mean age was 67.9 ± 16.9 years, and 79.4% were female. Compared with the age- and sex-matched cohort of patients with symptomatic TR, those with asymptomatic TR tended to have lower

comorbidities and biomarkers of end-organ damage (**Table 1**). In addition, they had lower estimated perioperative risk based on risk scores for tricuspid valve surgery: the median TRI-SCORE was 1, and the LaPar clinical risk score was 3, indicating predicted operative mortality of 2% and 4%, respectively. By contrast, for the age- and sex-matched cohort of symptomatic TR, the median TRI-SCORE was 4, and the LaPar clinical risk score was 6, indicating predicted operative mortality of 8% and 9%, respectively. Similarly, the TR parameters and the degree of RV remodeling and dysfunction were significantly worse in patients presenting with symptomatic TR (**Table 2**). There was good intraobserver and interobserver agreement for the echocardiographic parameters. A selected few are shown in Supplemental Figure 1.

Over a median follow-up time of 7.3 years (IQR: 3.5-11.3 years) in the asymptomatic TR cohort, tricuspid valve surgery was done in 9 (2.8%) patients, and there were 132 deaths (40.6%). The median survival time was 9.9 years (95% CI: 7.9-12.7 years). By contrast, among the age- and sex-matched cohort of patients with symptomatic TR, tricuspid valve surgery was done in 45 patients (13.9%), and there were 150 (46.2%) deaths, with a median survival time of 4.4 years (95% CI: 2.8-5.9 years) over the study period. Mortality was significantly lower in the asymptomatic TR cohort in both unadjusted analysis (HR: 0.43 [95% CI: 0.31-0.61]; $P < 0.001$) and multivariable-adjusted analysis (HR: 0.37 [95% CI: 0.24-0.56]; $P < 0.001$) (**Figure 2**). This remains significant when analysis was stratified by tricuspid valve surgery at follow-up. The median survival time was 3.2 years (95% CI: 2.1-5.1 years) for symptomatic TR with no surgery, 6.9 years (95% CI: 5.6-9.0 years) for symptomatic TR with surgery, and 9.5 years (95% CI: 7.6-12.5 years) for asymptomatic TR with no surgery ($P < 0.001$ for joint test) (Supplemental Figure 2).

In a subset of the asymptomatic TR cohort who had BNP values within 6 months of the echocardiogram (n = 95), there was modest correlation between the echocardiographic parameters and the BNP levels (Supplemental Figure 3). The variables with the highest correlation were RVFWS ($r = 0.51$), TAPSE ($r = -0.43$), RVGLS ($r = 0.38$), and RVol ($r = 0.37$) (**Figure 3**). Similarly, in the overall cohort of the 325 asymptomatic TR patients, most of the echocardiographic parameters showed a significant association with all-cause mortality in both unadjusted and multivariable-adjusted analysis (**Table 3**). However, when the echocardiographic parameters were combined in a stepwise selection model, only RVFWS (HR per unit decrease = 1.11 (95% CI: 1.06-1.15; $P < 0.001$) and RVol (HR per 10 mL increase = 1.17 (95% CI: 1.10-1.24; $P < 0.001$) remained significant, indicating their superiority as independent predictors over all other parameters. EROA was evaluated separately from RVol in the model because of multicollinearity. Although EROA was also significant when we replaced RVol with EROA in the selection model, the RVol model was marginally better than the EROA model based on the Akaike information criterion and relative likelihood (**Table 3,** Supplemental Figure 4). The result was comparable with those of complete case analysis based on nonmissing values (Supplemental Table 2). Similarly, RVFWS and RVol were significant prognostic parameters among patients with symptomatic TR (Supplemental Table 3).

For the 2 key echocardiographic parameters, the optimal threshold for predicting 5-year mortality was RVFWS ≤−19% and RVol >45 mL (or 26 mL/m^2 when indexed to body surface area) (**Figure 4,** Supplemental

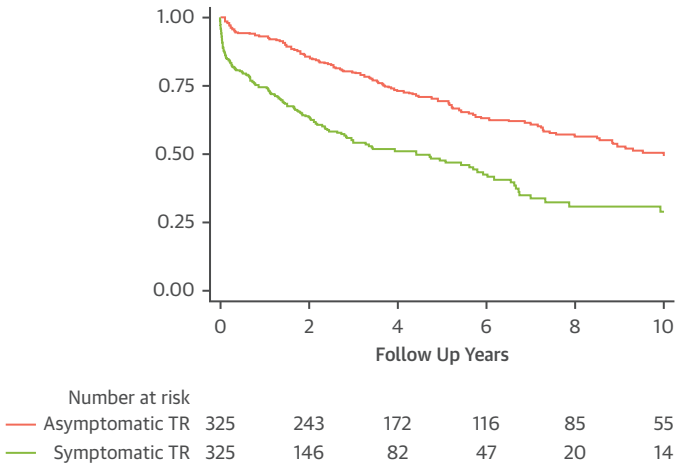
TABLE 2 Baseline Echocardiographic Characteristics of Asymptomatic TR Patients Compared With Age- and Gender-Matched Patients With Symptomatic TR

	Asymptomatic (n = 325)	Symptomatic (n = 325)	*P* Value
Tricuspid regurgitation parameters			
Vena contracta width, cm	0.77 (0.22)	1.24 (0.33)	<0.001
PISA radius, cm	0.65 (0.14)	0.86 (0.22)	<0.001
Effective regurgitant orifice area, cm^2	0.56 (0.26)	0.96 (0.60)	<0.001
Regurgitant volume, mL	46.7 (23.4)	89.7 (30.5)	<0.001
Right ventricle parameters			
Tricuspid valve annular diameter, cm	3.7 (0.9)	3.7 (0.8)	0.500
Basal diameter, cm	4.3 (0.8)	4.8 (0.9)	<0.001
Mid diameter, cm	3.3 (0.8)	3.8 (0.9)	<0.001
Longitudinal diameter, cm	6.2 (1.2)	7.7 (1.1)	<0.001
End-diastolic area index, cm^2/m^2	12.1 (3.5)	15.0 (4.1)	<0.001
End-systolic area index, cm^2/m^2	7.3 (3.0)	9.8 (3.2)	<0.001
TAPSE, mm	19.0 (5.1)	15.1 (5.1)	<0.001
Fractional area change	40.2 (10.7)	34.6 (11.4)	<0.001
Tricuspid annular systolic velocity,[a] cm/s	12.2 (3.4)	9.9 (3.4)	0.020
RV systolic pressure, mm Hg	44.4 (13.1)	55.9 (18.1)	<0.001
RVFWS	−20.2 (5.6)	−13.0 (4.9)	<0.001
RVGLS	−17.4 (4.4)	−11.5 (3.9)	<0.001
Right atrial parameters			
End systolic area index, cm^2/m^2	10.9 (3.8)	12.8 (5.2)	0.010
End systolic volume index, mL/m^2	33.0 (18.7)	43.4 (22.2)	0.003
RA reservoir strain	25.8 (10.6)	15.9 (7.4)	<0.001
Estimated right atrial pressure,[a] mm Hg	7.7 (4.4)	9.2 (5.0)	0.030
Left ventricle parameters			
LV end diastolic volume index, mL/m^2	44.7 (14.1)	41.0 (18.0)	0.020
LVEF	59.5 (5.2)	58.5 (6.0)	0.020
LA end systolic volume index, mL/m^2	32.7 (12.5)	39.7 (17.3)	<0.001

Values are n (%), unless otherwise indicated. Areas and volume measurements were indexed to body surface area. [a]Tricuspid annular systolic velocity (n = 156) and estimated right atrial pressure (n = 182) were not considered for multiple imputations because of high missing values.

LA = left atrium; LV = left ventricle; LVEF = left ventricle ejection fraction; PISA = proximal isovelocity surface area; RA = right atrium; RV = right ventricle; RVFWS = right ventricle free wall strain; RVGLS = right ventricle global longitudinal strain; TAPSE = tricuspid annular plane systolic excursion; other abbreviation as in **Table 1**.

FIGURE 2 Unadjusted Kaplan-Meier Survival Curve of Cohort of Asymptomatic Tricuspid Regurgitation as Compared With Age- and Sex-Matched Cohort of Symptomatic Tricuspid Regurgitation



Abbreviation as in Figure 1.

Figure 5). The sensitivity, specificity, and area under the curve for these thresholds were 0.74, 0.69, and 0.72 for RVFWS; 0.77, 0.68, and 0.76 for RVol; and 0.55, 0.89, and 0.66 for combination of the 2 thresholds, respectively. The distribution of these abnormal thresholds (ie, risk factors) in the cohort was 137 (42.2%) with no risk factor, 114 (35.1%) with only 1 risk factor (either of the 2), and 74 (22.8%) with both risk factors. Compared with patients with no risk factor (ie, RVFWS ≥−19% and RVol <45 mL), the rate of mortality was significantly higher for those with 1 risk factor (HR: 3.2 [95% CI: 1.9-5.6]; $P < 0.001$) or both risk factors (HR: 6.4 [95% CI: 3.6-11.6]; $P < 0.001$) (Figure 5). By contrast, having both risk factors was associated with significantly higher mortality compared with 1 risk factor alone (HR: 2.0 [95% CI: 1.31-3.05]; $P = 0.001$). The 5-year survival rates were 93% (95% CI: 86%-96%), 65% (95% CI: 55%-74%), and 38% (95% CI: 26%-49%) for no risk factor, 1 risk factor, and 2 risk factors, respectively. In multivariable-adjusted analysis, compared with the symptomatic TR cohort, mortality was lower for asymptomatic TR with no risk factor (HR: 0.10 [95% CI: 0.04-0.29]; $P < 0.001$) or 1 risk factor (HR: 0.29 [95% CI: 0.14-0.58]; $P = 0.001$) but was similar for asymptomatic TR with 2 risk factors (HR: 1.11 [95% CI: 0.56-2.19]; $P = 0.76$).

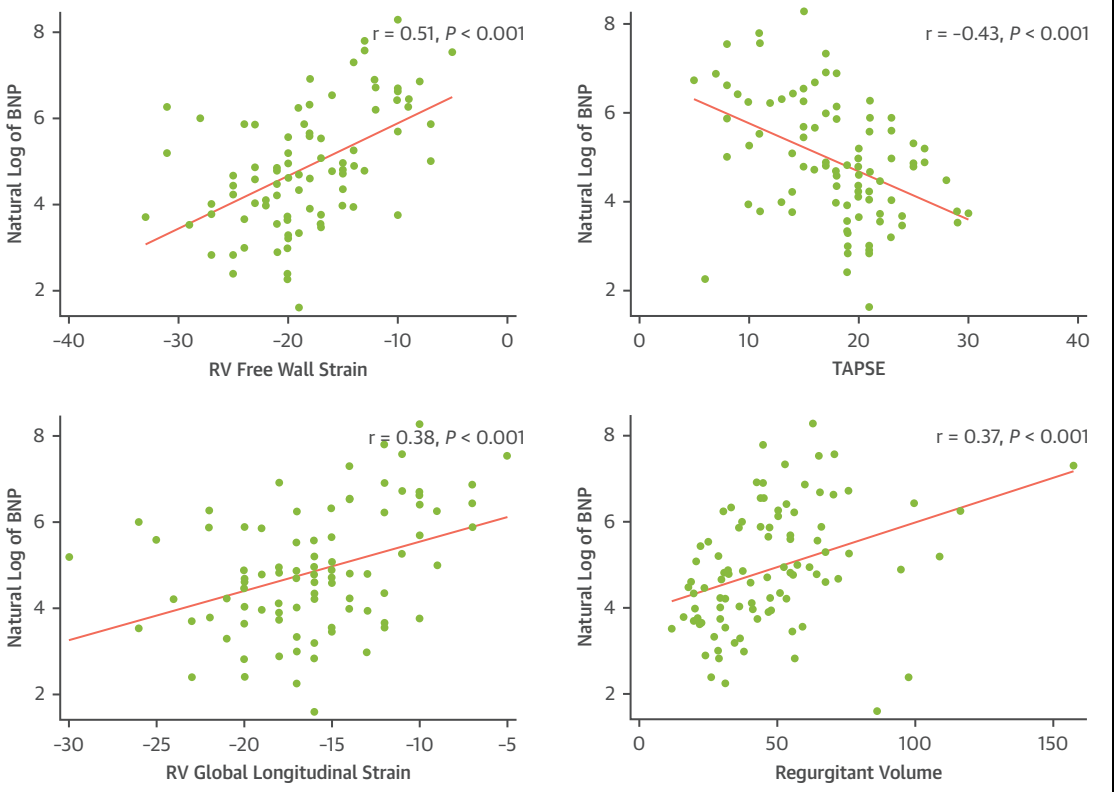
DISCUSSION

Our analysis highlights several clinically important findings for the assessment and management of asymptomatic TR. We showed that patients with asymptomatic TR have a favorable clinical profile, lower estimated operative risk, and better overall survival compared with patients presenting with symptomatic TR. Furthermore, we identified echocardiographic parameters, notably, RVFWS and RVol, that correlated with a biomarker of myocardial stress (ie, BNP) and significantly predicted long-term survival among patients with asymptomatic TR. Hence, serial evaluation of these 2 parameters may inform optimal timing for early intervention among patients with asymptomatic TR.

Accumulating evidence continues to show that TR is a strong predictor of excess morbidity and mortality independently of traditional risk factors and irrespective of symptom status.[2,18] Yet, isolated TR surgery is rarely performed.[4,7] In our analysis, TR surgery was performed in only 2.8% of the asymptomatic TR cohort despite the high rate of mortality (40.6%) over a median follow-up time of 7.3 years. This is partly caused by historical underestimation of the clinical impact of TR and the scarcity of data to inform clinical guidelines.[5,19] When performed, isolated TR surgery is usually delayed until symptom onset.[8] However, this is associated with worse procedural complications, including high operative mortality and poor long-term outcomes.[6-8,20] A plausible explanation for this poor outcome includes the subjective nature of symptom assessment, which may not be reported until late in the disease process, when end-organ damage and high-risk comorbidities have developed. The symptomatic TR cohort in our analysis had a predicted operative mortality of 8% to 9% compared with 2% to 4% in the asymptomatic cohort. In addition, the symptomatic cohort had a worse degree of RV remodeling and dysfunction at the time of visit, which may remain irreversible despite tricuspid valve surgery.[21] The irreversible RV dysfunction unequivocally contributes to the poor long-term survival in these patients.[21] The majority of the symptomatic TR cohort in the study were considered to be at very high or prohibitive risk for surgery at the time of presentation and were medically treated, with a median survival time of 3.2 years. In a small subset of this cohort (13.8%) who underwent isolated tricuspid valve surgery, the median survival time (6.9 years) remained lower than in the overall asymptomatic cohort (9.9 years). These results underscore the need for early intervention before the development of severe RV dysfunction and/or clinical symptoms.

It is therefore imperative to identify early markers of worse outcomes among patients with asymptomatic TR to inform the optimal timing for early

FIGURE 3 **Correlation Between Echocardiographic Parameters and BNP**



Only the top 4 correlations are shown. BNP = B-type natriuretic peptide; *r* = Pearson correlation coefficient; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion.

intervention. In our analysis, multiple echocardiographic parameters showed a modest correlation with a biomarker of myocardial stress (ie, BNP) and significantly predicted long-term survival in patients with asymptomatic TR. However, RVFWS and RVol were the best predictors of survival over and beyond other echocardiographic parameters. RVFWS ≤−19% and RVol >45 mL (or 26 mL/m^2 when indexed to body surface area) were the optimal discriminatory thresholds for mortality, and, given their prognostic implications, it is reasonable to consider intervention when either of these criteria is met, because these groups of patients have acceptable operative risk and will likely benefit from intervention. However, when both criteria are met, intervention should be strongly considered because the combination of both criteria has very good specificity (89%) and can be used to rule in for intervention. Notably, asymptomatic TR patients who met both criteria have survival that is as poor as that in the symptomatic TR cohort; yet, their operative risk is likely lower. Hence, they represent a group that is likely to benefit most from surgery.

There is currently a lack of data to guide early TR intervention. The ACC/AHA valve guidelines have no Class 1 recommendation for isolated TR surgery, and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guideline gave a Class 1 recommendation for isolated TR surgery only in patients with clinical symptoms.[5,19] However, in a prior analysis from our group, we showed that early surgery before the development of TR-related symptoms is associated with better in-hospital and long-term outcomes.[22] Although both the ACC/AHA and the ESC/EACTs guidelines recommended consideration of RV dilation or dysfunction as criteria for intervention in asymptomatic TR, the optimum threshold for intervention based on these parameters is unknown or poorly defined because of limited data. In our analysis, we showed that RV

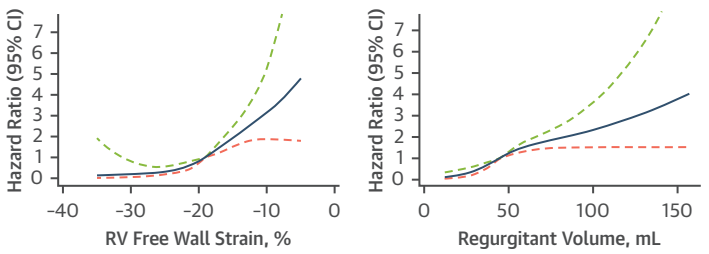
TABLE 3 Association of Echocardiographic Parameters With All-Cause Mortality

	Univariate Model		Multivariable-Adjusted Model[a]		Stepwise Selection Model[b]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Tricuspid regurgitation parameters						
Vena contracta width, per 0.1 cm	1.14 (1.07-1.23)	<0.001	1.12 (1.05-1.21)	0.001		
PISA radius, per 0.1 cm	1.39 (1.27-1.52)	<0.001	1.43 (1.28-1.59)	<0.001	–[c]	
EROA, per 0.1 cm^2	1.14 (1.09-1.19)	<0.001	1.14 (1.09-1.20)	<0.001	1.09 (1.03-1.15)[d]	0.002
Regurgitant volume, per 10 mL	1.21 (1.16-1.27)	<0.001	1.22 (1.15-1.29)	<0.001	1.17 (1.10-1.24)[d]	<0.001
Right ventricle parameters						
Tricuspid annular diameter, cm	1.39 (1.15-1.67)	0.001	1.24 (0.99-1.55)	0.050		
Basal diameter, cm	1.26 (1.04-1.52)	0.020	1.21 (0.97-1.51)	0.090		
Mid diameter, cm	1.21 (0.98-1.48)	0.080	1.25 (1.02-1.53)	0.030		
Longitudinal diameter, cm	0.92 (0.80-1.06)	0.250	0.94 (0.80-1.11)	0.490		
End diastolic area index, cm^2/m^2	1.08 (1.03-1.13)	0.001	1.10 (1.05-1.16)	<0.001	–[c]	
End systolic area index, cm^2/m^2	1.13 (1.08-1.19)	<0.001	1.17 (1.11-1.24)	<0.001		
TAPSE, mm	0.94 (0.91-0.98)	0.001	0.91 (0.87-0.96)	<0.001		
Fractional area change, %	0.96 (0.94-0.98)	<0.001	0.95 (0.93-0.97)	<0.001	0.99 (0.97-1.01)	0.200
Tricuspid annular systolic velocity, cm/s (n = 156)	0.95 (0.86-1.06)	0.340	0.98 (0.87-1.09)	0.670	–[e]	
Right ventricle systolic pressure, mm Hg	1.01 (1.00-1.03)	0.010	1.01 (0.99-1.02)	0.090		
RVFWS, %	1.13 (1.09-1.17)	<0.001	1.14 (1.10-1.18)	<0.001	1.11 (1.06-1.15)[d]	<0.001
RVGLS, %	1.10 (1.05-1.15)	<0.001	1.10 (1.05-1.15)	<0.001	–[c,d]	
Right atrial parameters						
End systolic area index, cm^2/m^2	1.10 (1.06-1.14)	<0.001	1.07 (1.03-1.12)	0.002	–[c]	
End systolic volume index, per 10 mL/m^2	1.18 (1.10-1.27)	<0.001	1.12 (1.03-1.22)	0.006		
RA reservoir strain,[e] %	0.93 (0.91-0.96)	<0.001	0.94 (0.91-0.97)	<0.001		
Estimated RA pressure, mm Hg (n = 182)	1.05 (1.00-1.10)	0.060	1.02 (0.97-1.07)	0.490	–[f]	

[a]Variables included in the multivariable-adjusted model were age, sex, race, cause of TR, history of cardiac surgery, TR surgery during follow-up, glomerular filtration rate, LVEF, diabetes, hypertension, and prior vascular event. Each echocardiographic parameter was evaluated separately in this model. [b]The stepwise selection model was adjusted for the same covariate as the multivariable-adjusted model and used a backward stepwise selection algorithm to select from echocardiographic parameters that were significant from the multivariable-adjusted model (except those tagged [c] or [f]). Echocardiographic parameters retained in the final model were regurgitant volume, fractional area change, RVFWS, and RA strain. Parameters with missing value for the last column represent those excluded from the final model by the selection algorithm because they did not meet the statistical requirement for the final model (ie, *P* exclusion = 0.20; *P* inclusion = 0.10). [c]Variables not included in the final stepwise selection model because of multicollinearity (variance inflation factor >10). [d]EROA and regurgitant volume were evaluated separately in the stepwise model because of multicollinearity. The regurgitant volume model was marginally better based on Akaike Information Criterion (AIC) and relative likelihood (RL) of 1,210 and 0.95, respectively, compared with 1,216 and 0.05, respectively for the EROA model. Similarly, the model with RVFWS (AIC: 1,200, RL >0.99) was better than with RV global strain (AIC: 1,220, RL <0.01). [e]The effect of RA reservoir strain varies over time. Estimates for the interaction with time were 1.03 (95% CI: 1.01-1.05) and 1.03 (95% CI: 1.01-1.05) in univariate and multivariable-adjusted models, respectively. [f]Variables not included in the final stepwise selection model because of large number of missing values.

EROA = effective regurgitant orifice area; other abbreviations as in Tables 1 and 2.

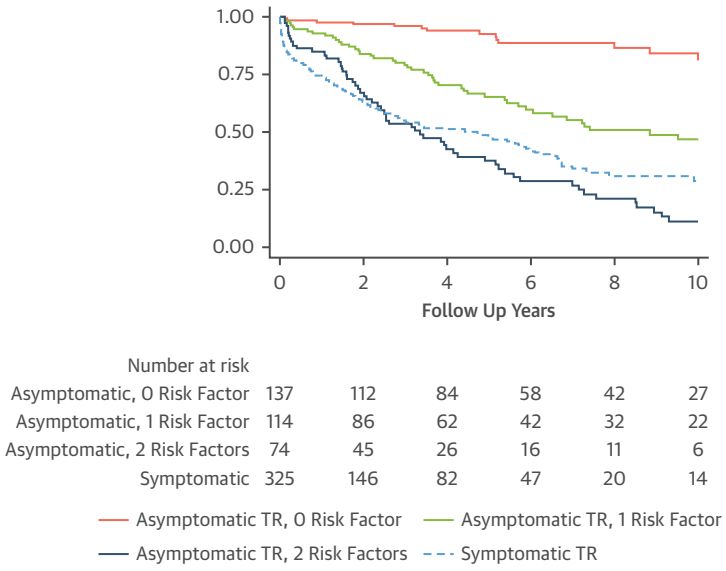
FIGURE 4 HR for Mortality



By values of right ventricle free wall strain (reference −19%) and regurgitant volume (reference 45 mL). Abbreviation as in Figure 3.

dilation alone is an inferior predictor of outcome in asymptomatic TR after adjustment for other clinical variables. A similar observation was also reported in a prior study involving a large cohort of patients with secondary TR where RV dilation, unlike RV systolic dysfunction, did not independently predict outcome.[23] By contrast, whereas multiple parameters of RV function predicted mortality independently of clinical variables in our analysis, RVFWS emerged as the best marker of RV function. This, in addition to prior studies,[24,25] indicates that RVFWS should be considered the first-line parameter for risk prediction among all markers of RV function in patients with TR. Although thresholds for many of the other RV function parameters are frequently used to define RV dysfunction for the purpose of intervention, the

FIGURE 5 **Unadjusted Kaplan-Meier Survival Curve**



By number of risk factors in the asymptomatic TR cohort. The risk factors were RV free wall strain ≤−19% and regurgitant volume >45 mL. Survival curve for age- and sex-matched symptomatic cohort is included for comparison. Abbreviations as in Figures 1 and 3.

guidelines rightfully acknowledge their limitations, including constraints related to RV complex geometry, their variability in image acquisition, and their use as markers of late stages of valve disease.[5,19] Thus, the 2 guidelines favor the evaluation of RV strain as an early marker of RV dysfunction even though the optimum threshold is unknown. Prihadi et al[25] showed that an RVFWS threshold of −23% was superior to TAPSE and FAC in predicting mortality among patients with TR. However, this threshold was based on a 97.5th percentile value of healthy volunteers without significant TR.[26] Extending on their result, we showed that a threshold of −19% represents the optimal threshold for mortality prediction in asymptomatic TR.

The published reports on the prognostic value of TR parameters reported mostly on EROA, with limited data on TR RVol.[2,27,28] In contrast to our finding, a prior study by Topilsky et al[2] suggested that EROA may be superior to RVol in patients with isolated TR. However, the discrepancy between the 2 findings may be explained by differences in patient characteristics. For instance, Topilsky et al[2] included patients with a wide array of TR severity, ranging from trivial to severe TR (59.8% with EROA and RVol of zero), atrial fibrillation (44%) with expected beat-to-beat variation in RVol, and high rate of diuretic use (41% among those with severe TR) that may have an impact on the RVol. These patient characteristics could either pose technical challenges to RVol assessment or make it an unreliable marker of severity and outcome within a cohort of patients with severe TR. However. these patient characteristics were absent in our cohort. In addition, compared with RVol, EROA measurement is less robust because the dynamic nature of the regurgitation, both in volume and in time, is rarely taken into account in the EROA measurement. Volumetric assessment, by contrast, is less affected by these limitations and is preferred in cases of significant dynamic change in regurgitation.[12] Although a few studies have proposed an RVol cutoff ranging from 20 to 30 mL for severe TR,[29,30] none of them have evaluated the optimal threshold in patients with asymptomatic TR, in whom the competing risk of death is less and mortality is thus more likely to occur at higher TR severity. Although an RVol of 45 mL was recommended as the threshold for severe TR in the American Society of Echocardiography guideline, this was based on extrapolation from mitral regurgitation data,[31] and the guideline acknowledges that the optimum threshold for severe TR is unknown, indicating the need for further confirmation. Our study, representing the first detailed analysis of predictors of outcome in asymptomatic TR, provides the first

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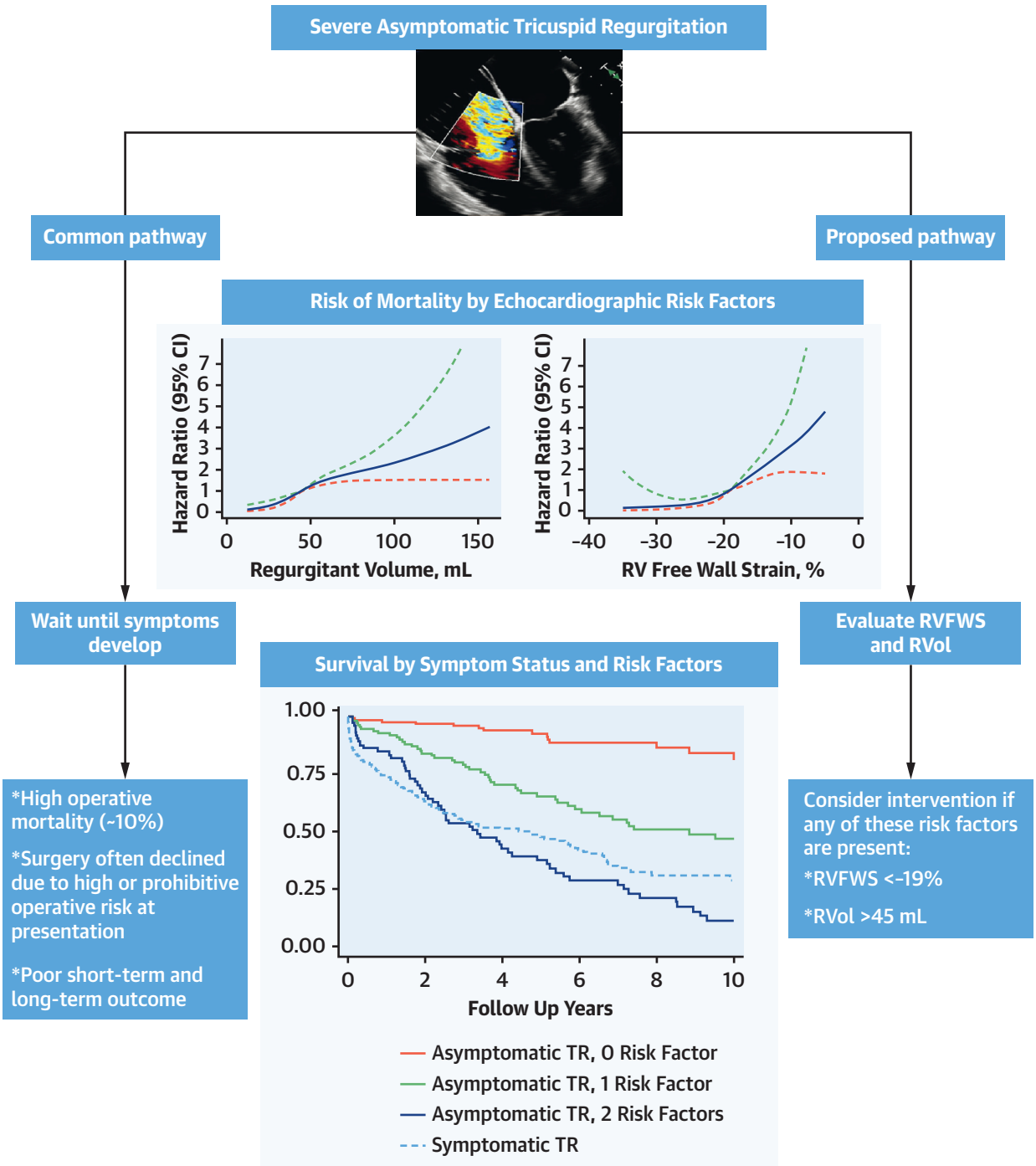
CENTRAL ILLUSTRATION **Timing of Intervention in Severe Asymptomatic Tricuspid Regurgitation**



Akintoye E, et al. J Am Coll Cardiol Img. 2023;16(1):13-24.

RV = right ventricle; RVFWS = right ventricle free wall strain; RVol = tricuspid regurgitant volume; TR = tricuspid regurgitation.

clinical evidence that an echocardiographic threshold of 45 mL (as recommended) has discriminatory prognostic value in TR.

The current study has multiple clinical implications. It underscores the importance of shifting the timing for isolated TR surgery to earlier stages of the disease because waiting for symptom onset is associated with poor prognosis.[5] In addition, RVFWS and TR RVol were identified as the key echocardiographic parameters to guide patient selection for early interventions; therefore, these parameters should be routinely assessed as part of the standard of care for patients with moderate or severe TR (**Central Illustration**). On the other hand, right ventricle dilation, although currently recommended as a criterion for intervention in the guidelines, has no significant prognostic utility in asymptomatic TR.[5,19] Last, surgery should continue to be considered for symptomatic patients with low to moderate surgical risk, inasmuch as it was shown to be beneficial in this study and was based on our prior analyses,[22,32] whereas patients at a very high or prohibitive surgical risk may be considered for transcatheter therapies, in addition to optimal medical therapy, if ongoing transcatheter trials continue to show benefit.[3,33-35]

STUDY LIMITATIONS. This study has some limitations that need to be considered. First, it was a single-center observational study with potential inherent areas of bias. To limit bias, we used a systematic approach to patient selection, ensured that measurements were made by trained personnel blinded to patient outcome, determined statistical methods a priori, and performed sensitivity analyses to evaluate the robustness of our result. Second, the study included patients over a long time period, which might have been a potential source of bias because of the evolution of treatment options. Third, only a few TR surgeries (2.8%) were performed in the asymptomatic cohort, with 1 death during follow-up. Hence, the impact of surgery could not be statistically evaluated in this cohort. Fourth, the subset of patients with asymptomatic TR included in the final analysis represented only a small fraction of the total TR patients in the database. However, the likely reason is that most patients with asymptomatic TR were less likely to be referred for care; therefore, the true real-world prevalence of asymptomatic TR is probably underestimated. Highlighting the need for early intervention in asymptomatic TR therefore represent the first step in identifying the true prevalence of asymptomatic TR in the general population. Last, it was not possible to quantify the amount of symptoms attributable to TR in the symptomatic TR cohort because the patients in it had other comorbidities that may have contributed to their symptoms.

CONCLUSIONS

Asymptomatic TR patients have a lower estimated operative risk and better prognosis compared with those with symptomatic TR. TR intervention should be done early in the course of the disease, preferably before symptom onset, when operative mortality is low and irreversible right ventricle dysfunction has not occurred. Echocardiographic parameters, most notably RVFWS and RVol, can be serially monitored to inform optimal timing for early TR intervention. Further research is however needed to evaluate the impact of surgery or transcatheter therapies in patients with asymptomatic TR who meet the proposed thresholds.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Intervention for severe tricuspid regurgitation should be done early in the course of the disease before the development of symptoms, irreversible right ventricle dysfunction, or end-organ damage. Serial evaluation of RVFWS and RVol can provide prognostic information and may inform optimal timing for early intervention. The authors propose that intervention should be considered when the RVFWS is ≤−19% or when the RVol is >45 mL.

TRANSLATIONAL OUTLOOK: There is need for additional research to evaluate the long-term impact of surgery or transcatheter therapies in patients with asymptomatic tricuspid regurgitation who meet the proposed thresholds.

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KEY WORDS asymptomatic, early intervention, survival, tricuspid regurgitation

APPENDIX For supplemental figures and tables, please see the online version of this paper.