Prevalence and Clinical Implications of Tricuspid Valve Prolapse Based on Magnetic Resonance Diagnostic Criteria

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ABSTRACT

BACKGROUND Tricuspid valve prolapse (TVP) is an uncertain diagnosis with unknown clinical significance because of a scarcity of published data.

OBJECTIVES In this study, cardiac magnetic resonance was used to: 1) propose diagnostic criteria for TVP; 2) evaluate the prevalence of TVP in patients with primary mitral regurgitation (MR); and 3) identify the clinical implications of TVP with regard to tricuspid regurgitation (TR).

METHODS Forty-one healthy volunteers were analyzed to identify normal tricuspid leaflet displacement and propose criteria for TVP. A total of 465 consecutive patients with primary MR (263 with mitral valve prolapse [MVP] and 202 with nondegenerative mitral valve disease [non-MVP]) were phenotyped for the presence and clinical significance of TVP.

RESULTS The proposed TVP criteria included right atrial displacement of ≥ 2 mm for the anterior and posterior tricuspid leaflets and ≥ 3 mm for the septal leaflet. Thirty-one (24%) subjects with single-leaflet MVP and 63 (47%) with bileaflet MVP met the proposed criteria for TVP. TVP was not evident in the non-MVP cohort. Patients with TVP were more likely to have severe MR (38.3% vs 18.9%; $P < 0.001$) and advanced TR (23.4% of patients with TVP demonstrated moderate or severe TR vs 6.2% of patients without TVP; $P < 0.001$), independent of right ventricular systolic function.

CONCLUSIONS TR in subjects with MVP should not be routinely considered functional, as TVP is a prevalent finding associated with MVP and more often associated with advanced TR compared with patients with primary MR without TVP. A comprehensive assessment of tricuspid anatomy should be an important component of the preoperative evaluation for mitral valve surgery. (J Am Coll Cardiol 2023;81:882–893) © 2023 by the American College of Cardiology Foundation.

In the early 1970s, morphologic studies described isolated cases of replacement of the tricuspid leaflets' fibrosa by a loose myxomatous tissue, with an increase in the leaflets' area, which became voluminous and bulging into the right atrium during systole.[1] These abnormalities were found mostly in patients with mitral valve prolapse (MVP), suggesting an underlying connective tissue disorder.[2,3] Initial prevalence rates of tricuspid valve prolapse (TVP) were reported to be as high as 50% in patients with MVP.[2,4,5] However, these investigations diagnosed TVP empirically or extrapolating criteria for MVP.

With scarce published data since its initial description, TVP is an uncertain diagnosis with unknown clinical significance.[6-10] Conventionally, tricuspid regurgitation (TR) in patients with mitral valve (MV) disease is considered secondary to the left-sided heart disease, a manifestation of right ventricular remodeling following pressure and volume overload in the presence of normal tricuspid leaflets. Leaflet tethering and tricuspid annular dilatation are the main pathophysiological mechanisms involved in functional TR, with advanced TR being associated with poor outcomes.[11-14] The implications of

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structural tricuspid valve pathology in patients with primary mitral regurgitation (MR) have not been well studied thus far.

Noninvasive assessment of the tricuspid valve is challenging because of the variable anatomy, with thin leaflets as well as the anterior position of the right ventricle inside the chest. Two-dimensional transthoracic echocardiography has important limitations when assessing tricuspid valve anatomy because of the complex anatomy of the tricuspid annulus, with a saddle shape similar to that described for the mitral annulus.[15] The 3 leaflets can rarely be visualized simultaneously, and there is uncertainty regarding which of the leaflets is visualized in each view, with their assessment being highly dependent on the transducer angulation and rotation. Three-dimensional echocardiography is used at experienced centers to comprehensively assess tricuspid valve anatomy,[16] but it is not routinely performed because of a suboptimal transthoracic acoustic window, longer examination time, or insufficient expertise. As opposed to the limitations of echocardiography, cardiac magnetic resonance (CMR) can play a critical role in the evaluation of the tricuspid valve leaflets from potentially any view to reliably identify the affected leaflet(s).[17,18] Defined criteria for normal displacement of the leaflets toward the right atrium and a subsequent definition of TVP could ensure the consistency of the diagnosis and

establish its clinical impact. We hypothesize that TVP is not a sporadic pathology and that its prevalence in patients with myxomatous MV disease is important, with a potential role in progression to advanced TR in this population. The objectives of the present study were to use CMR to: 1) propose criteria for the diagnosis of TVP; 2) evaluate the prevalence and clinical characteristics of TVP in patients with primary MR; and 3) identify the clinical implications of TVP in terms of tricuspid valve function.

METHODS

To address the first objective of the study (propose criteria for the diagnosis of TVP), a cohort of 41 healthy volunteers were recruited and underwent a screening questionnaire to exclude any underlying history of cardiovascular disease. Volunteers were comprehensively evaluated using CMR to define normal tricuspid valve morphology and function. For objectives 2 and 3, we studied a cohort of patients with primary MR, who underwent CMR at the Houston Methodist Hospital (Houston, Texas) between 2009 and 2021 and were enrolled into a prospective observational CMR registry. Clinical data were obtained from a structured patient interview and/or review of

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

MR = mitral regurgitation

MV = mitral valve

MVP = mitral valve prolapse

TAD = tricuspid annular disjunction

TR = tricuspid regurgitation

TVP = tricuspid valve prolapse

FIGURE 1 Study Cohort

Subjects with primary MR and no previous repair/replacement MV who had a CMR exam between 2009-2021 (n = 756)

Other significant valvular disease associated (n = 127)

Other organic etiology of the tricuspid regurgitation (n = 24)

Cardiac device (pacemaker/implantable cardiac defibrillator) (n = 55)

Suboptimal image quality due to arrhythmia (n = 40)/breath-hold issues (n = 50)

Incomplete study for the assessment of the TV (n = 4)

Single-leaflet MV prolapse (n = 128)

Bileaflet MV prolapse (n = 135)

Nondegenerative primary MR (n = 202)

Healthy volunteer cohort (n = 41)

Flowchart describing patient selection for this study. CMR = cardiac magnetic resonance; MR = mitral regurgitation; MV = mitral valve; TV = tricuspid valve.
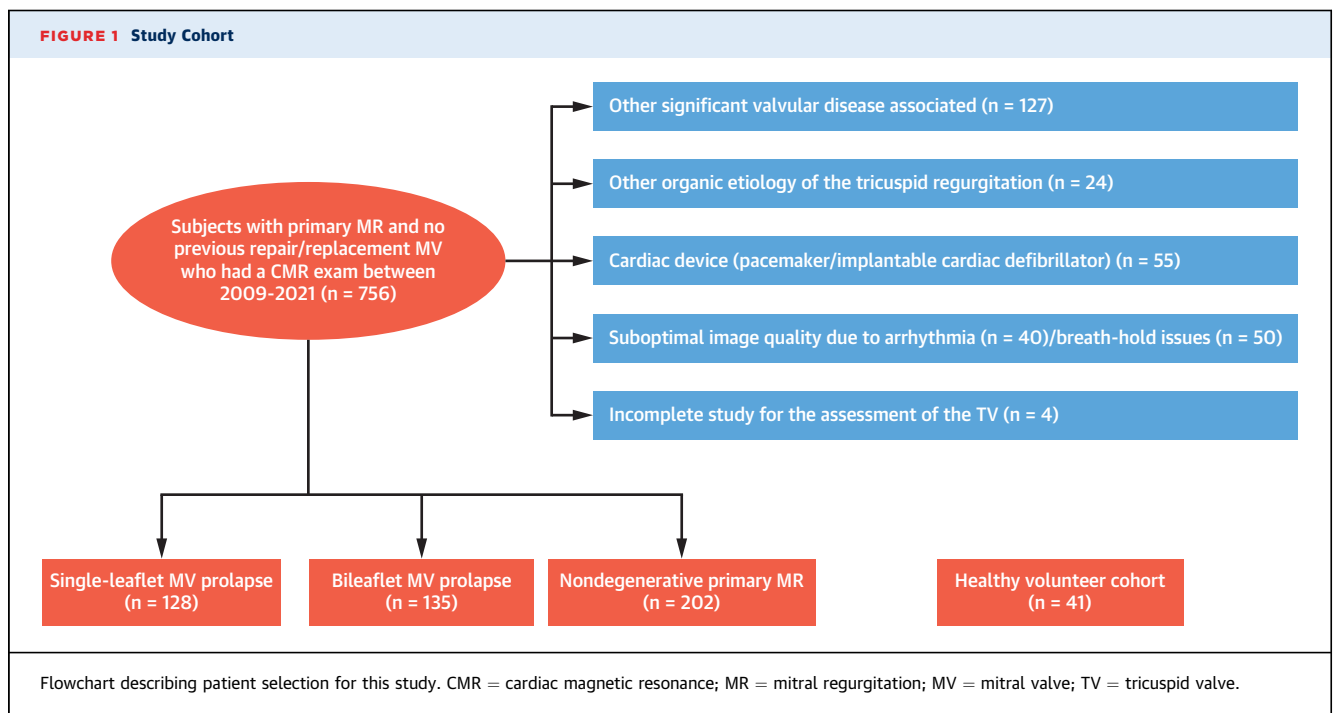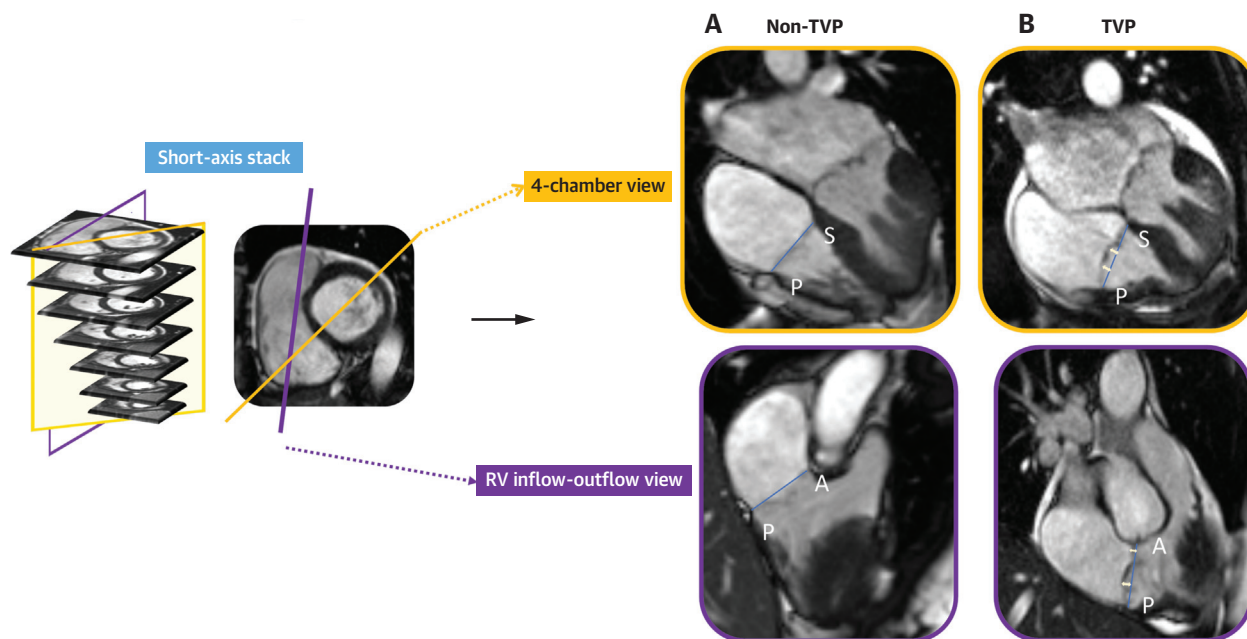
FIGURE 2   CMR Imaging Protocol for the Tricuspid Valve

A short-axis cine cardiac magnetic resonance (CMR) stack, covering the ventricles from the base to the apex, was used for alignment of the long-axis images. The anatomy of the tricuspid valve was evaluated in 2 cine CMR views, the 4-chamber and right ventricular (RV) inflow-outflow views. The leaflets shown in each view were the septal (S) and posterior (P) leaflets in the 4-chamber view and the anterior (A) and posterior leaflets in the RV inflow-outflow view, which was confirmed by cross-reference imaging. **(A)** Normal tricuspid leaflets with the coaptation point in the right ventricle, below the tricuspid annulus **(blue line)**, in a patient without tricuspid valve prolapse (TVP). **(B)** Displacement of all 3 leaflets, anterior, posterior, and septal, into the right atrium **(yellow double arrow)** in a patient with TVP.

available medical records. This investigation included patients with MVP and other primary MR (eg, rheumatic valve disease, mitral annular and leaflet calcification). We excluded patients with documented significant coronary artery disease, cardiomyopathies with reduced ventricular systolic function (left and/or right ventricular ejection fraction ≤40%), congenital heart disease, previous valvular surgery or repair, other organic TR, concomitant valvular disease greater than mild (except for MR and TR), or irregular rhythms that lead to inherent beat-to-beat variability in the severity of valvular regurgitation and ventricular volumes. Patients with suboptimal image quality or with incomplete scans for the assessment of the tricuspid valve were also excluded from the study (**Figure 1**). The study was approved by the Institutional Review Board at the Houston Methodist Research Institute.

CMR PROTOCOL AND ANALYSIS. CMR images were acquired using either 1.5-T or 3.0-T clinical scanners (Avanto, Aera, or Skyra, Siemens Healthineers). For anatomical and functional assessment, a standard examination comprising cine CMR acquisitions in the standard 2-, 3-, and 4-chamber views, right ventricular inflow-outflow view, and a short-axis stack of the ventricles was used, as previously described: steady-state free precession sequence with a flip angle of 65° to 85°, repetition time of 3 ms, echo time of 1.3 ms, in-plane spatial resolution of 1.7 to 2.0 × 1.4 to 1.6 mm, slice thickness of 6 mm with a 4-mm interslice gap, and temporal resolution of 35 to 40 ms.[19] Left and right ventricular volumes and myocardial mass were quantified via planimetry of endocardial and epicardial borders, on the short-axis cine CMR stack, covering the ventricular cavities from the base to the apex.

Morphology of the MV was evaluated on the formerly described cine images. In addition, a stack of high-resolution 3-chamber cine CMR was acquired using a steady-state free precession sequence with a flip angle of 45° to 85°, repetition time of 3 ms, echo time of 1.3 ms, reconstructed in-plane spatial resolution of 0.6 × 0.6 mm, slice thickness of 5 mm, and temporal resolution of 25 ms, as previously described.[19] The presence of mitral annular disjunction was evaluated in the 3 long-axis views:

2-chamber, 3-chamber, and 4-chamber views. The anatomy of the tricuspid valve was evaluated in 2 cine CMR views, the 4-chamber and right ventricular inflow-outflow views. The leaflets shown in each view were the septal and posterior leaflets in the 4-chamber view and the anterior and posterior leaflets in the right ventricular inflow-outflow view, which was confirmed by cross-reference imaging (Figure 2). To define normal valve morphology, the tricuspid valve was analyzed in a cohort of 41 healthy volunteers. Distance from the tricuspid annulus to the farthest point of the leaflet's body (septal, anterior, and posterior) toward the right atrium, at the end of systole, was measured in the 2 views: the 4-chamber and right ventricular inflow-outflow views. When the leaflet body was seen at the end-systole below the tricuspid annulus, toward the right ventricle cavity, the distance from the tricuspid annulus to the mid leaflet was measured, with a negative value. For the posterior leaflet, a mean of the 2 values from the 2 views was further used to define a threshold for a proposed definition of TVP. Tricuspid annular disjunction (TAD), defined as the maximum distance between the hinge point of the posterior tricuspid leaflet and the right ventricular myocardium, was measured in the 4-chamber and right ventricular inflow-outflow views (Supplemental Figure 1). We considered TAD present if a maximum distance of 1 mm or more was seen, in at least 1 view.

STATISTICAL ANALYSIS. Demographic and clinical characteristics are reported as frequencies and proportions for categorical variables and as median (IQR) for continuous variables. Distributions of maximum leaflet displacement are expressed as mean ± SD, median (IQR), and range (minimum to maximum). Cutoffs of the maximum leaflet displacement to discriminate TVP were explored and determined by the mean + 1.96 SDs in the group of normal volunteers. Differences across groups were determined using Student's *t*-test or the Kruskal-Wallis test for continuous variables. Multivariable generalized linear models for a binary outcome with log link were conducted to determine factors associated with the TVP (defined by all 3 thresholds), as well as advanced TR (defined as having moderate or severe TR). Univariable and multivariable ratios are reported. Given the small number of advanced TR events, separate multivariable models were adjusted by different combination of the imaging parameters to avoid overfitting. The selection of variables for the multivariable models was conducted using the least absolute shrinkage and selection operator method with the cross-validation selection option and clinical importance of the covariates.[20,21] Briefly, all variables

TABLE 1 Demographic, Clinical, and Imaging Characteristics of the Normal Healthy Volunteer Cohort (N = 41)

Demographic and clinical characteristics	
Age, y	35.0 (31.0-44.0)
Female	17 (41.5)
Race/ethnicity	
Caucasian	23 (56.1)
African American	1 (2.4)
Hispanic	5 (12.2)
Asian	10 (24.4)
Unknown/other	2 (4.9)
Body surface area, m²	1.8 (1.7-2.0)
Heart rate, beats/min	68 (63-78)
Systolic blood pressure, mm Hg	123 (112-130)
Diastolic blood pressure, mm Hg	82 (62-88)
Hypertension	0 (0.0)
Hyperlipidemia	12 (46.2)
Family history of coronary artery disease	8 (33.3)
Diabetes	0 (0.0)
Smoking	1 (9.1)
Family history of sudden cardiac death	0 (0.0)
Cardiac magnetic resonance findings	
LVEDV, mL	132 (119-159)
LVEDVi, mL/m²	76 (66-82)
LVESV, mL	47 (39-62)
LVESVi, mL/m²	27 (21-30)
LVSV, mL	86 (77-104)
LVSVi, mL/m²	49 (43-55)
LVEF, %	64 (61-68)
LAV, mL	73 (64-81)
LAVi, mL/m²	39 (35-45)
Myocardial mass, g	93 (77-122)
MA 4-chamber diameter, mm	31.0 (30.0-32.0)
MA 3-chamber diameter, mm	26.3 (24.0-28.0)
MA 2-chamber diameter, mm	33.6 (31.7-37.0)
TA 4-chamber diameter at end-diastole, mm	30.2 (28.0-32.8)
TA maximal diameter, mm	35.4 (33.5-38.7)
TA 4-chamber diameter at mid-systole, mm	31.0 (28.8-33.3)
RVEDV, mL	150 (130-184)
RVEDVi, mL/m²	87 (74-97)
RVESV, ml	71 (52-88)
RVESVi, mL/m²	37 (30-45)
RVSV, mL	87 (78-100)
RVSVi, mL/m²	48 (44-55)
RVEF, %	55 (53-60)
RV basal diameter, mm	44.1 (42.3-48.0)
RV mid diameter, mm	41.8 (37.4-44.2)
RV longitudinal diameter, mm	83.2 (79.0-89.0)
RV anteroposterior diameter, mm	67.9 (64.0-74.0)
RV septal to lateral diameter (short-axis), mm	34.6 (29.5-37.3)
RV sphericity index	0.5 (0.5-0.6)
RV eccentricity index	2.0 (1.8-2.3)
RA area, cm²	20.1 (18.8-23.0)

Values are median (IQR) or n (%). No corrections for multiple testing were applied.

LAV = left atrial volume; LAVi = left atrial volume indexed; LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume indexed; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVi = left ventricular end-systolic volume indexed; LVSV = left ventricular stroke volume; LVSVi = left ventricular stroke volume indexed; MA = mitral annular; RA = right atrial; RV, right ventricular; RVEDV = right ventricular end-diastolic volume; RVEDVi = right ventricular end-diastolic volume indexed; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVESVi = right ventricular end-systolic volume indexed; RVSV = right ventricular stroke volume; RVSVi = right ventricular stroke volume indexed; TA = tricuspid annular.

TABLE 2 Distribution of Maximum Leaflet Displacement in the Healthy Volunteer Cohort

Septal leaflet displacement, mm	
Mean ± SD	0.25 ± 1.4
Median (IQR)	0.0 (0.0 to 1.0)
Anterior leaflet displacement, mm	
Mean ± SD	−1.40 ± 1.7
Median (IQR)	−1.2 (−2.8 to 0.0)
Posterior leaflet displacement, mm	
Mean ± SD	−0.60 ± 1.4
Median (IQR)	−0.5 (−1.3 to 0.0)

used in the univariable analysis were assessed using the least absolute shrinkage and selection operator program, which suggested good initial models that included the variables with the highest probability of being a risk factor. During the modeling process, the potential risk factors were discussed with senior clinicians with extensive clinical experience in the field to ensure the biological plausibility and clinical importance of the selected covariates. To avoid overfitting, some variables that were significant in the univariate analysis but insignificant in multivariable modeling were not selected in the final model if their exclusion did not affect the diagnostic performance of the final model, which was determined by a nonsignificant likelihood ratio test result and the area under the receiver-operating characteristic curve. P values and 95% CIs were not adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible. All analyses were performed using Stata version 17.0 (StataCorp). P values of <0.05 were considered to indicate statistical significance.

RESULTS

TVP DEFINITION. Baseline characteristics and CMR parameters for the healthy volunteer cohort are summarized in Table 1. The mean age was 35 years, and women constituted 41.5% of the cohort. Values for peak leaflet displacement from the annular plane in the healthy volunteer cohort are summarized in Table 2. The peak leaflet displacement was 0.25 ± 1.4 mm for the septal leaflet, −1.40 ± 1.7 mm for the anterior leaflet, and −0.60 ± 1.4 mm for the posterior leaflet. Therefore, peak displacement exceeding the mean by 1.96 SDs of the healthy volunteer cohort, rounded to whole numbers, are proposed as criteria for TVP: ≥2 mm for the anterior and posterior leaflets and ≥3 mm for the septal leaflet (Central Illustration).

TVP IN SUBJECTS WITH PRIMARY MR. A total of 756 subjects with primary MR were analyzed. After applying the exclusion criteria, 263 patients with MVP (128 with single-leaflet and 135 with bileaflet MVP) and 202 patients with non-MVP primary MR were included in the study cohort. Baseline characteristics and CMR parameters for the primary MR cohort are summarized in Table 3. Patients in the non-MVP cohort had less severe MR (29% moderate or severe MR compared with 71% in the single-leaflet MVP cohort and 68% in the bileaflet MVP cohort; $P < 0.001$) and smaller left ventricular volume (end-diastolic volume 68 mL/m² vs 100 mL/m² in the single-leaflet MVP cohort and 104 mL/m² in the bileaflet MVP cohort; $P < 0.001$) compared with patients with MVP. Right ventricular volume was also smaller in patients without MVP (end-diastolic volume 70 mL/m² vs 89 mL/m² in the single-leaflet MVP cohort and 93 mL/m² in the bileaflet MVP cohort; $P < 0.001$) compared with the MVP cohort. There was a significant increase in displacement of the 3 leaflets in patients with MVP compared with the healthy volunteer cohort and patients with non-MVP primary MR (Table 4, Supplemental Table 1). Within the MVP cohort, patients with bileaflet MVP had higher tricuspid leaflet displacement values compared with those with single-leaflet MVP. A total of 31 subjects (24%) with single-leaflet MVP and 63 patients (47%) with bileaflet MVP met the proposed criteria for TVP. However, none of the non-MVP primary MR subjects had associated TVP. The relationship among TVP, TAD, and mitral annular disjunction is detailed in the Supplemental Appendix.

CHARACTERISTICS ASSOCIATED WITH TVP. Characteristics of patients with TVP are detailed in Supplemental Table 2. Compared with patients without TVP, subjects with TVP had more severe MR (regurgitation volume 48 mL vs 28 mL; $P < 0.001$), larger end-diastolic mitral annuli (anteroposterior diameter 38 mm vs 32 mm; $P < 0.001$), and increased left atrial volumes (76 mL/m² vs 62 mL/m²; $P < 0.001$). Subjects with TVP also had increased left ventricular volume compared with patients without TVP (end-diastolic volume 104 mL/m² vs 85 mL/m²; $P < 0.001$), but similar left ventricular systolic function was noticed in the 2 groups (left ventricular ejection fraction 66%; $P = 0.23$). Patients with TVP had larger tricuspid annuli (maximum 4-chamber diameter 38.6 mm vs 36 mm; $P < 0.001$), larger right ventricular volumes (end-diastolic volume 93 mL/m² vs 80 mL/m²; $P < 0.001$), and lower right ventricular ejection fractions (54% vs 56%; $P = 0.001$). However, body surface area, extent of MVP (bileaflet vs single-leaflet MVP), severity of MR, mitral and tricuspid annular diameter, and left ventricular end-

CENTRAL ILLUSTRATION Tricuspid Valve Prolapse Using Cardiac Magnetic Resonance
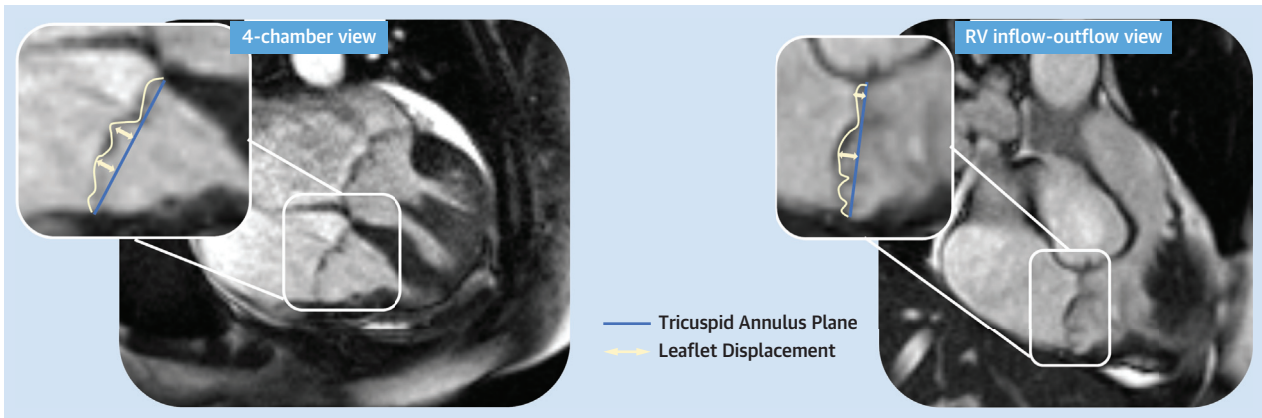
Tricuspid valve anatomy was evaluated in 2 cine cardiac magnetic resonance views, the 4-chamber and right ventricular (RV) inflow-outflow views. Tricuspid valve prolapse was defined as right atrial displacement **(yellow double arrow)** of ≥2 mm for the anterior and posterior leaflets and ≥3 mm for the septal leaflet, above the level of the tricuspid annulus **(blue line)**. MR = mitral regurgitation; MVP = mitral valve prolapse.

diastolic volume were the only independent factors associated with the presence of TVP. The risk for having TVP appeared not to be associated with the increase in age in our study population after being adjusted for other covariates in the multivariable analysis (**Table 5**). Although RV volumes and ejection fraction were associated with TVP on univariable analysis, the relationship did not persist on multivariable analysis (right ventricular end-diastolic volume, $P = 0.12$; ejection fraction, $P = 0.47$). **Figure 3** illustrates the relationship between TVP and MR severity in the 4 mentioned cohorts (healthy volunteers, patients with non-MVP MR, those with single-leaflet MVP, and those with bileaflet MVP).

TVP AND TR. TR volume (16.0 mL vs 11 mL; $P < 0.001$) and TR fraction (19% vs 14%; $P = 0.001$) were higher in patients with TVP compared with those with non-TVP primary MR, with a higher proportion of moderate or severe TR in the TVP group (23.4% vs 6.2%; $P < 0.001$) (Supplemental Table 2). The presence of TVP, MR volume, and right and left ventricular end-diastolic volumes were associated with increased TR severity (**Table 6,** Supplemental Table 3). No

association between right ventricular ejection fraction and TR severity was found. **Figure 4** illustrates the relationship between TR severity and TVP in patients with different degrees of MR severity.

DISCUSSION

To the best of our knowledge, this is the first study to propose CMR criteria for the definition of TVP on the basis of peak tricuspid valve leaflet displacement in healthy volunteers. We evaluated the prevalence of TVP in patients with primary MR (both MVP and non-MVP) and further assessed the potential role of TVP in developing TR in this population. The main findings can be summarized as follows: 1) atrial displacement of ≥2 mm for the anterior and posterior tricuspid valve leaflets and ≥3 mm for the septal tricuspid valve leaflet indicates TVP; 2) TVP is a prevalent disease, with all 3 leaflets affected in approximately 50% of subjects with bileaflet MVP, and is associated with more severe MVP and MR, suggesting an advanced stage of the myxomatous disease; and 3) in this population, TR should not be routinely considered secondary to left heart disease, and a primary

TABLE 3   Primary Mitral Regurgitation Cohort Demographic, Clinical, and Imaging Characteristics

	Non-MVP (n = 202)	Single-Leaflet MVP (n = 128)	Bileaflet MVP (n = 135)	P Value
Demographic and clinical characteristics				
Age, y	69.0 (62.0-75.7)	63.5 (57.3-70.0)	58.1 (44.6-67.2)	<0.001
Female	152 (75.2)	50 (39.1)	68 (50.4)	<0.001
Race/ethnicity				
Caucasian	121 (59.9)	113 (88.3)	112 (83.0)	
African American	31 (15.3)	3 (2.3)	4 (3.0)	<0.001
Hispanic	8 (4.0)	2 (1.6)	10 (7.4)	
Asian	7 (3.5)	6 (4.7)	5 (3.7)	
Unknown/other	35 (17.3)	4 (3.1)	4 (3.0)	
Body surface area, m^2	1.9 (1.7-2.0)	2.0 (1.7-2.1)	1.9 (1.7-2.0)	0.03
Heart rate, beats/min	71 (63-80)	67 (60-74)	70 (64-78)	0.01
Systolic blood pressure, mm Hg	137 (122-152)	133 (124-142)	133 (122-144)	0.053
Diastolic blood pressure, mm Hg	74.0 (64.0-81.0)	74.5 (68.0-82.0)	72.0 (66.0-79.0)	0.34
eGFR, mL/min/m^2	68.6 (54.4-88.2)	77.4 (69.5-90.9)	81.9 (71.3-90.4)	<0.001
Hypertension	167 (83.1)	64 (50.0)	47 (35.3)	<0.001
Hyperlipidemia	140 (69.3)	57 (44.5)	39 (29.3)	<0.001
Family history of coronary artery disease	88 (45.4)	41 (32.8)	42 (32.1)	0.02
Diabetes	67 (33.5)	9 (7.1)	5 (3.8)	<0.001
Smoking	46 (24.1)	34 (27.6)	17 (13.2)	0.01
Family history of sudden cardiac death	30 (15.1)	16 (12.6)	12 (9.2)	0.30
Peripheral arterial disease	6 (4.0)	0 (0.0)	1 (1.5)	0.13
History of atrial fibrillation	6 (5.0)	1 (4.2)	3 (13.6)	0.27

disease of the tricuspid valve leaflets must be excluded because of the possible implications in clinical management.

TVP ENTITY. Early studies reported a prevalence of TVP as high as 50% in patients with MVP.[2,4,5] However, results were limited by very small cohorts and technical limitations of 2-dimensional echocardiography at the time. Since its initial description, no other study had addressed TVP until recently, when Lorinsky et al[22] analyzed TVP prevalence in a large population, using 2-dimensional echocardiography to evaluate tricuspid valve morphology. They identified TVP in 0.4% of the general population, with 75% of patients with TVP also having MVP. It is notable that the investigators analyzed only patients with TVP reported in the clinical echocardiography report, potentially excluding a large group of subjects with unreported TVP. Furthermore, to confirm the presence of TVP, the tricuspid valve was evaluated in the parasternal short-axis view, and a cutoff of >2 mm was used to define TVP. However, the variability of echocardiographic imaging planes is well acknowledged, and so are the limitations regarding tricuspid valve leaflets assessment when visualized in only 1 bidimensional view. Another recent study using CMR to analyze the prevalence of TAD in patients with mitral annular disjunction, demonstrated a prevalence of TVP of 42% in patients with MVP and mitral

annular disjunction.[23] Nevertheless, in that study, TVP was empirically defined as ≥2 mm displacement of any part of the leaflets beyond the tricuspid annulus. The present study is the first to use CMR to propose a definition for TVP on the basis of analysis of a cohort of healthy volunteers and to assess the prevalence of TVP in a large cohort of subjects with primary MV disease. In our study, the tricuspid valve was assessed in 2 views, the 4-chamber and right ventricular inflow-outflow views, accounting for the 3-dimensional geometry of the tricuspid annulus, with the higher hinge points being visualized in the right ventricular inflow-outflow view (anteroseptal and posterolateral tricuspid annular points). This approach increases the specificity of the diagnosis of TVP. We specifically did not use a right ventricular 2-chamber view, because it would traverse through the low points of the tricuspid annulus and could lead to "pseudo-displacement" of the tricuspid leaflets into the right atrium. Tricuspid leaflet displacement in the healthy volunteers had higher values when evaluated in the 4-chamber view, as expected if we consider the lower points of the tricuspid annulus represented in this view. Therefore, we propose a peak atrial displacement of ≥2 mm for the anterior and posterior leaflets in any view and ≥3 mm for the septal leaflet as thresholds to identify TVP. Surprisingly, results from Lorinsky et al[22] showed that the highest values of atrial displacement of the tricuspid

TABLE 3 Continued			
	Non-MVP (n = 202)	**Single-Leaflet MVP** (n = 128)	**Bileaflet MVP** (n = 135)	**P Value**
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Cardiac magnetic resonance findings				
Mitral valve leaflet flail	—	63 (49.6)	22 (16.3)	<0.001
Mitral regurgitation severity				<0.001
Mild	144 (71.0)	37 (29.0)	44 (33.0)	
Moderate	40 (20.0)	44 (34.0)	55 (41.0)	
Severe	18 (9.0)	47 (37.0)	36 (27.0)	
MA 3-chamber diameter, mm	26.0 (3.7-29.0)	3.5 (3.2-4.0)	4.0 (3.6-4.5)	<0.001
TA 4-chamber diameter at end-diastole, mm	31.0 (28.0-33.0)	32.0 (29.1-36.1)	33.3 (30.0-38.0)	<0.001
TA maximal diameter, mm	35.0 (31.0-38.0)	37.7 (34.8-41.0)	38.0 (33.8-42.0)	<0.001
TA 4-chamber diameter at mid-systole, mm	31.0 (27.0-34.0)	33.5 (30.8-37.4)	34.0 (31.0-38.4)	<0.001
RV basal diameter, mm	45.3 (40.1-48.6)	46.2 (42.0-50.3)	46.4 (41.7-50.7)	0.32
RV mid diameter, mm	36.7 (32.5-40.2)	39.3 (35.0-43.4)	38.4 (35.0-44.0)	0.003
RV longitudinal diameter, mm	77.6 (70.0-81.7)	79.0 (72.0-84.2)	78.4 (72.4-85.9)	0.004
RV anteroposterior diameter, mm	75.7 (69.7-79.7)	73.5 (64.0-80.0)	73.0 (66.4-81.0)	0.01
RV septal to lateral diameter (short-axis), mm	32.7 (28.7-36.6)	35.0 (31.0-41.0)	33.8 (29.0-37.8)	0.03
RV sphericity index	0.6 (0.5-0.6)	0.6 (0.5-0.6)	0.6 (0.5-0.6)	0.85
RV eccentricity index	2.3 (1.9-2.7)	2.1 (1.7-2.4)	2.2 (1.9-2.6)	0.002
LVEDV, mL	130 (103-166)	196 (143-239)	190 (155-235)	<0.001
LVEDVi, mL/m^2	68 (57-88)	100 (84-121)	104 (90 121)	<0.001
LVESV, mL	39 (27-58)	63 (48-89)	65 (53-83)	<0.001
LVESVi, mL/m^2	21 (15-30)	35 (26-44)	37 (30-44)	<0.001
LVSV, mL	91 (72-110)	126 (99-153)	122 (99-154)	<0.001
LVSVi, mL/m^2	49 (39-58)	66 (57-79)	69 (56-79)	<0.001
LVEF, %	69 (62-75)	65 (62-70)	65 (61-69)	<0.001
LAV, mL	102 (78-136)	131 (104-186)	141 (102-189)	<0.001
LAVi, mL/m^2	53 (42-73)	69 (53-92)	76 (55-99)	<0.001
Myocardial mass, g	121 (95-145)	123 (97-158)	108 (85-143)	0.04
RVEDV, mL	127 (106-163)	170 (139-205)	164 (136-208)	<0.001
RVEDVi, mL/m^2	70 (57-84)	89 (75-102)	93 (79-105)	<0.001
RVESV, mL	53 (40-69)	77 (60-100)	79 (58-100)	<0.001
RVESVi, mL/m^2	29 (21-35)	41 (32-49)	44 (34-53)	<0.001
RVSV, mL	75 (61-94)	90 (78-107)	88 (75-109)	<0.001
RVSVi, mL/m^2	40 (34-49)	47 (42-54)	49 (43-56)	<0.001
RVEF, %	59 (53-64)	55 (50-59)	54 (50-57)	<0.001
RA area, cm^2	19 (16-23)	21 (19-24)	22 (18-25)	<0.001
TR volume, mL	10 (3-18)	12 (6-23)	14 (4-24)	0.01
TR fraction, %	12 (5-20)	15 (6-24)	15 (5-25)	0.10

Values are median (IQR) or n (%). No corrections for multiple testing were applied.

eGFR = estimated glomerular filtration rate; MVP = mitral valve prolapse; TR = tricuspid regurgitation; other abbreviations as in Table 1.

valve leaflets in normal subjects were found in the parasternal short-axis view, which theoretically displays the highest tricuspid valve hinge points. This discrepancy can be explained, as mentioned, by the variability of the transducer angulation and the ambiguity regarding which of the tricuspid valve leaflets is visualized in each echocardiographic view. It is noteworthy that for reasons of specificity, we considered TVP to be present if all 3 leaflets were involved. This finding might have excluded cases of single-leaflet tricuspid prolapse, and the clinical significance of this entity was not analyzed in the present study. Another important consideration is the visualization of the tricuspid valve leaflets in each of the CMR views. In this study, cross-reference was used to determine the evaluated leaflets. Variability in slice positioning among laboratories and different technologists exists. Thus, the leaflet attached to the right ventricular free wall on a 4-chamber view can be either the posterior or anterior tricuspid valve leaflet, and the anterior portion of the tricuspid valve on the right ventricular inflow-outflow view could be an anterior or septal leaflet. However, we do not expect high variability in normal peak atrial displacement between the 2 leaflets in each of the views, and we presume that the same thresholds can be used. Further studies are required to confirm this hypothesis.

TABLE 4 Distribution of Maximum Leaflet Displacement in the 4 Defined Cohorts

	Healthy Volunteers (n = 41)	Non-MVP MR (n = 202)	Single-Leaflet MVP (n = 128)	Bileaflet MVP (n = 135)	P Value
Septal leaflet displacement, mm					
Mean ± SD	0.3 ± 1.4	0.4 ± 1.4	2.4 ± 2.0	3.1 ± 2.1	<0.001
Median (IQR)	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)	2.0 (1.0 to 4.0)	3.0 (2.0 to 4.0)	<0.001
Range	−3.5 to 3.8	−4 to 4.7	−2 to 8	−2 to 10	−
Anterior leaflet displacement, mm					
Mean ± SD	−1.4 ± 1.7	−1.2 ± 1.8	0.6 ± 2.4	2.2 ± 2.5	<0.001
Median (IQR)	−1.2 (−2.8 to 0.0)	−1.0 (−2.0 to 0.0)	0.0 (−1.0 to 2.0)	2.0 (0.0 to 4.0)	<0.001
Range	−5 to 1	−7 to 4	−5 to 6	−3 to 10	−
Posterior leaflet displacement, mm					
Mean ± SD	−0.6 ± 1.4	−0.2 ± 1.4	1.6 ± 2.3	2.9 ± 2.2	<0.001
Median (IQR)	−0.5 (−1.3 to 0.0)	0.0 (−1.0 to 0.5)	1.5 (0.0 to 3.1)	3.0 (1.5 to 4.5)	<0.001
Range	−5 to 1	−5 to 4	−2.5 to 8.6	−2 to 8.5	−

No corrections for multiple testing were applied.

MR = mitral regurgitation; MVP = mitral valve prolapse.

ASSOCIATION OF TVP WITH MV DISEASE. Myxomatous MV disease is a rather prevalent pathology, with a poor prognosis in the presence of significant MR, left ventricular dysfunction, or left ventricular

TABLE 5 Clinical and Cardiac Magnetic Resonance Characteristics Associated With Tricuspid Valve Prolapse

	Univariable		Multivariable	
	RR (95% CI)	P Value	RR (95% CI)	P Value
Demographic and clinical characteristics				
Age	0.98 (0.97-1.00)	0.01	−	−
Male	1.44 (1.01-2.07)	0.045	1.19 (0.74-1.90)	0.48
Body surface area	0.41 (0.19-0.90)	0.03	0.21 (0.07-0.65)	0.01
Cardiac magnetic resonance findings				
Mitral valve leaflet flail	0.75 (0.52-1.10)	0.14	−	−
Bileaflet MVP	4.97 (3.40-7.27)	<0.001	2.84 (1.78-4.54)	<0.001
MR volume	1.01 (1.01-1.02)	<0.001	1.03 (1.01-1.04)	<0.001
MR fraction	1.02 (1.01-1.03)	<0.001	−	−
Mitral annular diameter[a]	2.34 (1.95-2.81)	<0.001	1.79 (1.29-2.49)	<0.001
TA largest diameter	1.06 (1.03-1.09)	<0.001	1.05 (1.01-1.10)	0.02
LVEDV	1.00 (1.00-1.01)	<0.001	0.99 (0.98-1.00)	0.02
LVESV	1.01 (1.00-1.01)	0.01	−	−
LVEF	0.99 (0.96-1.01)	0.23	0.98 (0.95-1.01)	0.23
Left atrial volume	1.005 (1.00-1.02)	0.001	0.99 (0.99-1.00)	0.32
RVEDV	1.004 (1.00-1.01)	0.003	1.01 (1.00-1.01)	0.12
RVESV	1.01 (1.00-1.01)	0.001	−	−
RVEF	0.96 (0.94-0.98)	0.001	1.01 (0.98-1.05)	0.48
Right atrial area	1.02 (0.99-1.06)	0.14	0.96 (0.92-1.01)	0.11
Right atrial diameter	1.00 (0.80-1.26)	0.97	−	−
			Estimated AUC = 0.85	

The RR was obtained from the generalized linear model for binary outcome with log link. Variables included in the multivariable models were selected using the least absolute shrinkage and selection operator method and based on clinical importance. No corrections for multiple testing were applied. The number of patients with complete data for the models' variables was 440. [a]Mitral annular anteroposterior diameter

AUC = area under the curve; RR = risk ratio; other abbreviations as in Tables 1 and 2.

scar.[24] TR associated with primary MR is conventionally considered secondary to right ventricular remodeling following pressure and volume overload and in the presence of structurally normal tricuspid leaflets.[25] However, several case reports have described associated TVP in patients with connective tissue disorders and myxomatous MV disease. A recent study including children with genotype-positive Marfan syndrome demonstrated a prevalence of 68.5% of TVP.[26] Subjects with TVP had a higher incidence of aortic root dilatation and MVP than patients without TVP, suggesting that TVP is an important marker of disease progression.[26] However, the investigators did not provide information about specific criteria used for TVP in these patients. To the best of our knowledge, no study has addressed the clinical implications of TVP in the adult population; nevertheless, it might suggest an advanced stage of myxomatous disease. In our cohort, TVP prevalence was significantly higher in the cohort of patients with bileaflet MVP compared with patients with single-leaflet MVP, suggesting a possible association with MVP severity. Furthermore, TVP was more prevalent in patients with severe MR compared with those with mild or moderate MR, independent of MVP severity, suggesting a possible associated hemodynamic impact of the increased left atrial pressures on right heart geometry. However, this was not evaluated in our study, and future studies (including echocardiography or right heart catheterization) are required to fully investigate this.
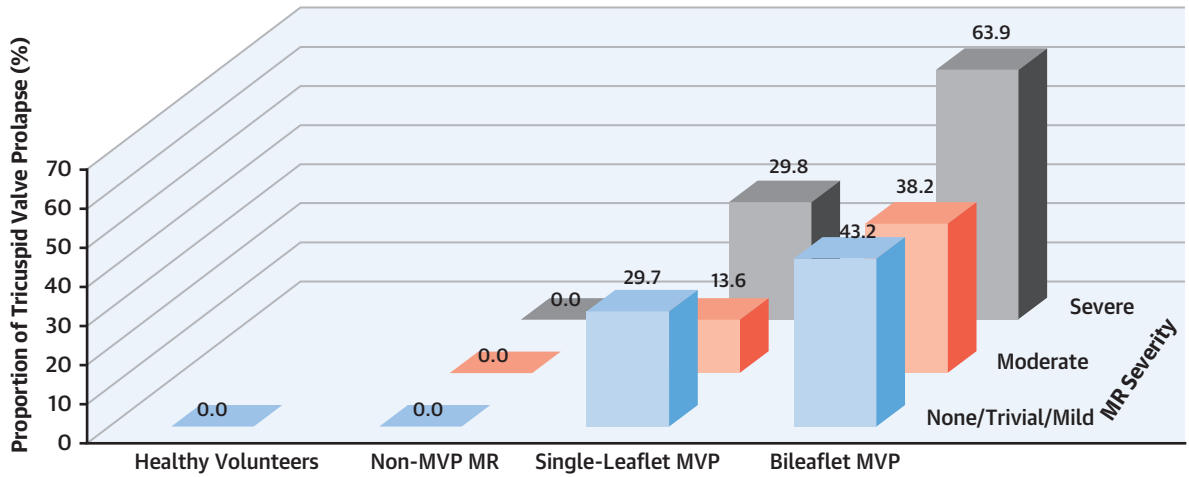
TVP AND VALVE FUNCTION. In this study, TVP subjects were more likely to have increased TR volumes. Although there is a general agreement that tricuspid

FIGURE 3 Prevalence of Tricuspid Valve Prolapse in Different Subgroups

MR Severity	Healthy Volunteers (n = 41)	Non-MVP MR (n = 202)	Single-Leaflet MVP (n = 128)	Bileaflet MVP (n = 135)
None/Trivial/Mild (n = 266)	41	144	37	44
Moderate (n = 139)	0	40	44	55
Severe (n = 101)	0	18	47	36

Bar chart showing the proportion of tricuspid valve prolapse in the 4 defined groups and by severity of the mitral regurgitation (MR). MVP = mitral valve prolapse.

FIGURE 4 Prevalence of Moderate or Severe Tricuspid Valve Regurgitation in Different Subgroups
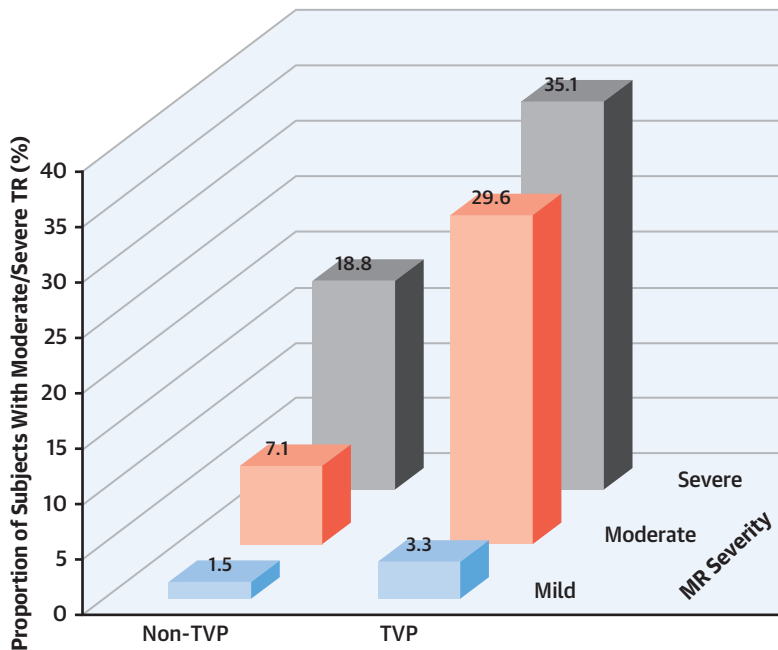
Bar chart showing the proportion of moderate or severe tricuspid regurgitation (TR) in the tricuspid valve prolapse (TVP) and non-TVP groups and by severity of mitral regurgitation (MR).

TABLE 6   Covariates Associated With Advanced Tricuspid Regurgitation Severity

Model A	Multivariable RR (95% CI)	P Value	Model B	Multivariable RR (95% CI)	P Value
TVP presence[a]	2.45 (1.26-4.75)	0.010	TVP presence	2.08 (1.05-4.12)	0.04
MR volume	1.01 (1.00-1.02)	0.003	MR volume	1.02 (1.01-1.04)	0.001
RVEDVi	1.04 (1.03-1.05)	<0.001	LVEDVi	1.07 (0.98-1.16)	0.14
RVEF	1.03 (0.97-1.08)	0.35	RVEDVi	1.16 (1.04-1.29)	0.01
	Estimated AUC = 0.93			Estimated AUC = 0.93	

[a]TVP was defined using the 3 described thresholds. Advanced tricuspid regurgitation was defined as moderate or severe tricuspid regurgitation. The RR was obtained from the generalized linear model for binary outcome with log link. Separate multivariable models were adjusted by different imaging parameters to avoid overfitting given the small number of advanced tricuspid regurgitation events. Variables included in the multivariable models were selected using the least absolute shrinkage and selection operator method and based on clinical importance. No corrections for multiple testing were applied. Model A: TVP presence + MR volume + RVEDVi + RVEF. Model B: TVP presence + MR volume + LVEDVi + RVEDVi.

TVP = tricuspid valve prolapse; other abbreviations as in **Tables 1 and 5**.

valve anatomy and right ventricular remodeling are closely related, in this study the presence of advanced TR was associated with higher right ventricular volume but not with right ventricular ejection fraction. These findings favor our hypothesis that TR in patients with TVP is related to the morphologic abnormalities of the valve, and the increase in right ventricular volume is a consequence of higher TR volume rather than a cause of TR. The presence of TVP is important when considering surgical planning. Current guidelines recommend concomitant tricuspid valve annuloplasty at the time of left-sided valve surgery in patients with severe TR or in cases of progressive TR and a dilated annulus of >40 mm (or >21 mm/m^2) or prior signs and symptoms of right-sided heart failure.[27,28] However, this recommendation is based on observational data, and the presence of TVP is not accounted for in the current guidelines when evaluating subjects with primary MR. A recent multicenter randomized trial assessed the impact of concomitant tricuspid annuloplasty at the time of MV surgery for correction of primary MR.[29] The investigators found that patients who underwent tricuspid annuloplasty had a lower incidence of reoperation for TR and lower progression of TR, but at the costs of significantly more complications (need for pacemaker implantation) and longer index hospitalization. Furthermore, in a post hoc analysis the investigators found that progression of TR occurred almost exclusively in patients with moderate TR and not in those with mild TR and annular dilatation, calling into question the indication for annuloplasty in the latter case.[29] In the present study, we found patients with TVP having larger tricuspid annuli, but not necessarily meeting the guideline criteria for tricuspid annuloplasty, and the management of this subgroup is currently controversial. Additional studies are needed to address the clinical significance of TVP in terms of surgical management in patients with MVP.

STUDY LIMITATIONS. Although CMR has the advantage of direct visualization of cardiac and valvular anatomy, the in-plane spatial resolution is lower than that of echocardiography, and the maximum displacement of the leaflets can be underestimated compared with the latter. Right ventricular afterload parameters (eg, pulmonary artery pressure) and its potential effect on TVP prevalence were not assessed in this study. However, the higher TVP prevalence in patients with MVP compared with patients without MVP across similar MR severity argues in favor of an underlying tricuspid valve pathology as opposed to a simple hemodynamic effect. Moreover, in this study, we did not compare imaging results with intraoperative findings. Further studies are needed to address the clinical significance of TVP in terms of surgical outcomes.

CONCLUSIONS

TR in subjects with MVP should not be routinely considered functional, as TVP is a prevalent finding associated with myxomatous MV disease. Bileaflet MVP and severe MR were associated with the presence of TVP, suggesting a more advanced stage of the myxomatous disease in this population. Additional consideration should be given to the tricuspid valve, particularly in patients undergoing surgical interventions of the MV, because of the possible implications of TVP in surgical planning.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: TVP is frequent in patients with myxomatous valve disease and has specific implications for surgical management of TR and MR.

TRANSLATIONAL OUTLOOK: Future studies are needed to establish the reproducibility of various cardiac imaging modalities for diagnosis of TVP.

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APPENDIX For supplemental methods as well as a supplemental figure and tables, please see the online version of this paper.