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ORIGINAL RESEARCH

Prevalence, Incidence, and Outcomes of Diastolic Dysfunction in Isolated Tricuspid Regurgitation

Perhaps Not Really "Isolated"?

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ABSTRACT

BACKGROUND In the absence of left-sided cardiac/pulmonary disease, functional tricuspid regurgitation (FTR) is referred to as isolated or idiopathic. Relationships between left ventricular diastolic dysfunction (DD) and FTR remain unknown.

OBJECTIVES The purpose of this study was to investigate the prevalence, incidence, and outcome of DD in patients with idiopathic FTR.

METHODS Adults without structural heart disease were identified. Severe DD was defined by ≥3 of 4 abnormal DD parameters (medial e', medial E/e', TR velocity, left atrial volume index) and ≥ moderate DD by ≥2. Propensity-score matching was performed (3:1) between each less-than-severe TR group and severe TR based on age, sex, body mass index, and comorbidities.

RESULTS Among 30,428 patients, FTR was absent in 73%, mild in 22%, moderate in 4%, and severe in 0.4%. In the propensity-matched sample, severe DD was present in 2%, 6%, 9%, and 13% patients, and ≥ moderate DD in 11%, 18%, 28%, and 48%, respectively ($P < 0.001$). The probability of heart failure with preserved ejection fraction using the H_2FPEF score increased with increasing FTR (median 29.7%, 45.5%, 61.4%, and 88.7%, respectively), as did the prevalence of impaired left atrial strain <24% (35%, 48%, and 69% in mild, moderate, and severe TR). Incident severe and ≥ moderate DD developed more frequently with increasing FTR (HR: 8.45 [95% CI: 2.60-27.50] and HR: 2.82 [95% CI: 1.40-5.69], respectively for ≥ moderate vs no FTR) over a median of 3.0 years. Findings were confirmed in patients without lung disease or right ventricular enlargement. Over a median of 5.0 years, patients with ≥ moderate FTR and DD had the greatest risk of worse outcomes (multivariable $P < 0.001$). The association between TR and adverse outcomes was significantly diminished in the absence of DD.

CONCLUSIONS Diastolic dysfunction, increased heart failure with preserved ejection fraction probability, and impaired left atrial strain are commonly present in patients with idiopathic FTR, suggesting that the latter may not be truly isolated. Patients with FTR without DD or heart failure are at increased risk of incident DD. Patients with FTR and DD display worse outcomes. (JACC Cardiovasc Imaging 2024;■:■–■) © 2024 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DD = diastolic dysfunction

FTR = functional tricuspid regurgitation

HFpEF = heart failure with preserved ejection fraction

LV = left ventricle/ventricular

RA = right atrium

RV = right ventricle/ventricular

TTE = transthoracic echocardiography

Secondary/functional tricuspid regurgitation (FTR) can occur with multiple cardiac and pulmonary diseases. FTR is common in patients with heart failure with preserved ejection fraction (HFpEF),[1-3] and can occur with right ventricular (RV) remodeling caused by postcapillary pulmonary hypertension (PH) or right atrial (RA) dilation.[4]

Multiple studies have evaluated etiologies of FTR in the general population, where FTR in the absence of left-sided valve disease, left ventricular (LV) systolic dysfunction, or PH was referred to as "idiopathic," "isolated," or more recently, "atrial secondary" TR when RV function and size are preserved.[5-8] Atrial fibrillation (AF) was found to be common in this setting,[5-7,9,10] but LV diastolic dysfunction (DD) was not adequately characterized, and the prevalence of DD (and HFpEF) in patients with isolated FTR remains unknown. Isolated TR is associated with increased morbidity and mortality,[11-13] but the mechanisms underlying this association or its potential dependence on DD remain unknown.

Exertional dyspnea and fatigue can be attributed to the valve lesion and the subsequent low output state in patients with TR, but these symptoms may also be caused by DD and underlying (occult) HFpEF, for which effective therapies are currently available beyond TR-specific interventions.[14,15] Atrial remodeling is common in patients with atrial secondary TR and may indicate the presence of a systemic proinflammatory process common to DD and HFpEF.[16-19] Therefore, patients with apparently isolated FTR may still have occult DD, which may become clinically evident over time. In this study, we aimed to investigate the prevalence of DD using resting echocardiography across the different severities of FTR; evaluate the incidence of DD at follow-up in these groups; and analyze outcomes of HF hospitalizations and all-cause mortality according to TR and DD status.

METHODS

STUDY POPULATION. This retrospective cohort study was approved by the Institutional Review Board. Patients evaluated at Mayo Clinic sites who had transthoracic echocardiograms (TTEs) from 2010 to 2021 were considered. Patients with chronic AF of more than 1 month before the TTE were excluded given the known relationship with TR, whereas those with new-onset AF (<1 month) were included (Supplemental Figure 1). Patients with other structural heart disease, including low ejection fraction (EF), enlarged LV, primary valve disease, > mild mitral leaflet calcification or regurgitation, any mitral stenosis, significant left-sided valve disease, primary cardiomyopathy, congenital heart disease, or regional wall motion abnormalities; pacemakers/defibrillators; connective tissue disease; primary tricuspid disease; absent TR grading; or no follow-up TTE ≥6 months were excluded (Supplemental Figure 1). Comorbidities were identified using the International Classification of Disease (ICD) codes. ICD codes for HF referred to HFpEF given the exclusion of current/prior low EF.

ECHOCARDIOGRAPHY. All patients underwent clinically indicated TTE, performed according to current guidelines and interpreted by level-III board-certified echocardiologists.[20] Diastolic function assessment was according to guidelines.[21] The presence of abnormal diastolic function (mitral medial e <7 cm/s, mitral medial E/e′ ratio >15 during sinus rhythm and >11 during AF, left atrial volume index (LAVI) >34 mL/m^2, TR velocity >2.80 m/s) was examined. For the purpose of this study analysis, irrespective of whether 2, 3, or 4 parameters were available, the presence of ≥3 of 4 abnormal diastolic function parameters was examined as a binary variable, referred to as "severe DD," whereas the presence of at least 2 of 4 abnormal DD parameters was examined as a separate binary variable and referred to as "≥ moderate DD," with the understanding that the number of abnormal DD parameters does not necessarily reflect severity of DD, and all patients with "severe DD" were included in the "≥ moderate DD" group. Details on dealing with missing data on identifying severe and ≥ moderate DD are in the Supplemental Methods.

Chamber size measurements were performed according to guidelines.[22] In the matched subset of patients (see the following text), measurements of RV end-systolic and end-diastolic areas and RV mid-ventricular diameter from RV-focused apical 4-chamber views were performed on the stored echocardiographic images by 2 readers (T.H., G.T.), and the fractional area change was calculated to assess RV function. RA size was measured from apical 4-chamber views at end-systole using the single-plane summation method. RV enlargement was defined as RV end-diastolic area >24 cm^2 in men or >20 cm^2 in women, and RV end-systolic area >15 cm^2 in men or >11 cm^2 in women. RA enlargement was defined as ≥39 mL/m^2 in men or ≥33 mL/m^2 in women, equivalent to ≥2 SD above the mean. Myocardial deformation analysis was performed off-line from 2-dimensional echocardiographic images

using commercially available software (Image Arena, TomTec Imaging Systems) by 4 observers (J.A.N., T.H., A.T., S.D.). LA and RA endocardial contours were traced from the apical 4-chamber views, and LA and RA reservoir strain were measured using the QRS interval as the fiducial point. Interobserver agreement for RV and RA measurements as well as LA and RA reservoir strain was assessed using the intraclass correlation coefficient in a random 10-patient sample. TR severity was classified as no/trivial, mild, moderate, or severe based on an integrative approach including assessment of RA size, inferior vena cava, hepatic vein flow, color flow Doppler (jet area, vena contracta [VC], flow convergence), density of the regurgitant jet, and whenever available, the proximal isovelocity surface area (effective regurgitant orifice area [EROA] and regurgitant volume).[23] Severe TR was further graded as massive or torrential when the continuous wave Doppler contour was dense and triangular, especially when low peak velocity also existed[24] (massive TR: VC width 14-20.9 mm, EROA 60-79 mm^2, or regurgitant volume 60-74 mL; torrential TR: VC width ≥21 mm, EROA ≥80 mm^2, or regurgitant volume ≥75 mL).[24]

PROBABILITY OF HFpEF USING THE CONTINUOUS H_2FPEF SCORE AND HFA-PEFF SCORE. To estimate the probability of HFpEF, the H_2FPEF continuous score was calculated in the study population as detailed in the Supplemental Methods.[25,26] Furthermore, the resting HFA-PEFF score was evaluated, using functional, morphological, and biomarker parameters to classify patients into high (5-6 points), intermediate (2-4 points), and lower likelihood scores (0-1 point).[27]

FOLLOW-UP. Patients without diagnosed HFpEF or ≥ moderate/severe DD at baseline (DD had to be absent; unknown DD was not eligible for this analysis) were followed using available TTEs for the development of ≥ moderate/severe DD, respectively, until last follow-up. In addition, patients without severe DD at baseline were followed for worsening DD, detailed in the Supplemental Methods. Patients with < moderate TR were followed for the development of incident ≥ moderate TR, and the association with DD at baseline was assessed. All patients were followed for outcomes of all-cause mortality and HF hospitalization. If patients had multiple HF hospitalizations, time to the first event was recorded (Supplemental Figure 2).

STATISTICAL ANALYSIS. Continuous variables are reported as median (IQR) and categorical variables as number (percentage). The Kruskal-Wallis and chi-square tests were used to compare variables between groups of different TR severity. Incidence rate was calculated as number of events divided by total follow-up time for all patients at risk. Patients who developed low EF before DD were censored at that time, while patients who did not develop low EF or DD were censored at last TTE follow-up.

In analyzing the association between TR severity and prevalent and incident DD, to account for baseline differences between TR groups, a propensity score was calculated using logistic regression (generalized linear method in the "MatchIt" package in R using greedy nearest neighbor matching) based on age, sex, body mass index, AF, hypertension, diabetes mellitus, sleep apnea, chronic lung disease, coronary artery disease, and HFpEF. No limits to matching distance were used. One separate score was used to match each less-than-severe TR group (no FTR, mild FTR, moderate FTR) in a 3:1 ratio to patients with severe FTR (total of 3 propensity scores) (Supplemental Figure 3). Because these patients were not matched based on diastolic function parameters, patients without DD at baseline who were eligible for analysis of incident severe and ≥ moderate DD were not necessarily matched between the groups. Thus, the propensity score matching was repeated for patients in the 3 TR groups at risk of severe DD. Finally, the process was repeated again for those at risk of ≥ moderate DD. Kaplan-Meier curves were used for survival analysis to evaluate the association between baseline TR severity and incident DD. Kaplan-Meier curves were used for survival analysis to evaluate the association between baseline TR severity and incident DD.

In the overall unmatched cohort, the association of TR with prevalent DD was examined using logistic regression with multivariable adjustment for baseline differences. Cox proportional hazards regression was used for multivariable survival analysis of incident severe and ≥ moderate DD. The association between ≥ moderate TR and clinical outcomes of all-cause mortality and rate of HF hospitalizations was further stratified by the presence or absence of DD (≥ moderate DD and severe DD separately) in the overall cohort. Furthermore, the association between DD at baseline and the future development of incident moderate/severe TR in patients with no/mild TR was evaluated using Kaplan-Meier curves and Cox regression. In patients with no/mild TR and no HFpEF or DD (≥ moderate DD and severe DD, separately) at baseline, the association between incident DD, as time dependent covariate, and the outcome of moderate/severe TR was evaluated. Patients without events were censored at last clinical follow-up. In all multivariable analyses, only variables with $P < 0.05$

TABLE 1 Baseline Characteristics of Patients With Different Severities of Functional Tricuspid Regurgitation

	No FTR (n = 22,331)	Mild FTR (n = 6,817)	Moderate FTR (n = 1,155)	Severe FTR (n = 125)	*P* Value
Age, y	58.4 (47.7-67.2)	64.0 (54.1-72.0)	67.7 (57.4-75.9)	58.9 (46.8-71.0)	<0.001
Age >65 y	6,992 (31)	3,228 (47)	684 (59)	49 (39)	<0.001
Women	10,659 (48)	3,803 (56)	782 (68)	101 (81)	<0.001
BMI, kg/m^2	29.1 (25.2-33.8)	27.6 (24.2-32.0)	27.0 (23.6-31.7)	26.5 (22.7-32.2)	<0.001
New-onset atrial fibrillation	956 (4)	572 (8)	177 (15)	13 (10)	<0.001
Hypertension	10,408 (47)	3,350 (49)	617 (53)	45 (36)	<0.001
Sleep apnea	4,850 (22)	1,334 (20)	219 (19)	19 (15)	<0.001
Diabetes mellitus	6,138 (27)	1,727 (25)	297 (26)	24 (19)	<0.001
Chronic lung disease	2,230 (10)	712 (10)	153 (13)	23 (18)	<0.001
HFpEF	818 (4)	311 (5)	119 (10)	20 (16)	<0.001
CAD	3,760 (17)	1,302 (19)	234 (20)	22 (18)	<0.001

Values are median (Q1-Q3) or n (%).

BMI = body mass index; CAD = coronary artery disease; FTR = functional tricuspid regurgitation; HFpEF = heart failure with preserved ejection fraction; TIA = transient ischemic attack.

on univariate analysis were entered into the model, and backward stepwise selection was used until only variables with $P < 0.05$ remained. Statistical analyses were performed with JMP Pro software version 16.2.0 (SAS Institute Inc) and R version 4.2.2. Two-sided values of $P < 0.05$ were considered significant.

RESULTS

Overall, 30,428 patients were included (median age 60 years [Q1, Q3: 49-69 years], 50% women, 6% had incident AF). Of those, 22,331 (73%) had no/trivial FTR, 6,817 (22%) had mild FTR, 1,115 (4%) had moderate FTR, and 125 (0.4%) had severe FTR (Supplemental Figure 4). Of patients with severe TR, 10 patients had massive TR and 1 patient had torrential TR. Baseline characteristics according to FTR severity is shown in **Table 1**. Patients with increasing TR severity were more likely women, had lower body mass index, and had more AF and HFpEF. Patients had on average 1.9 follow-up TTEs per patient. This translated to 0.72 follow-up TTEs per patient per year. To account for baseline differences, the primary analysis of prevalent and incident DD focused on matched groups, whereas results pertinent to the overall cohort were included in the Supplemental Results.

PREVALENCE OF DIASTOLIC DYSFUNCTION WITH TR IN MATCHED PATIENTS. After propensity-score matching, 375 patients of each less-than-severe FTR group were identified (**Table 2**). Baseline TTE data across the different TR severities are shown in **Table 3**. Severe and ≥ moderate DD were significantly more common with increasing severity of TR (**Tables 3 and 4**). The distribution of abnormal diastolic function parameters across the yes, no, and unknown categories of ≥ moderate/severe DD is shown in Supplemental Table 1.

HFpEF PROBABILITY ACCORDING TO THE CONTINUOUS H_2FPEF SCORE. The probability of HFpEF significantly increased with increasing FTR severity, with median score-based probabilities of 29.7%, 45.5%, 61.4%, and 88.7% in patients with no, mild, moderate, and severe FTR in the matched cohort, respectively ($P < 0.001$) (**Table 3**). Furthermore, impaired LA (<24%) and RA (<19.8%) strain was more common with increasing TR severity (**Table 3**).

RISK OF INCIDENT DIASTOLIC DYSFUNCTION WITH TR IN MATCHED PATIENTS. Due to baseline differences in patients at risk of severe DD with different TR severities (Supplemental Table 2), patients from each less-than-severe TR group were matched in a 3:1 ratio to 68 at-risk patients (with no HFpEF or severe DD at baseline) with severe FTR (Supplemental Table 3). Over median 2.6 years (Q1-Q3: 1.3-5.1 years), severe DD developed in 3 of 204 patients with no FTR (0.4 per 100 person-years), 12 of 204 patients with mild FTR (1.6 per 100 person-years), 28 of 204 patients with moderate FTR (3.5 per 100 person-years), and 8 of 68 patients with severe FTR (4.4 per 100 person-years). Duration of follow-up was similar across all groups ($P > 0.60$). Mild and moderate/severe FTR were associated with incident severe DD (HR: 3.79 [95% CI: 1.07-13.44] and 8.45 [95% CI: 2.60-27.50], respectively, vs no FTR; $P < 0.001$ for both) (**Figure 1**). Worsening DD results are shown in Supplemental Results and Supplemental Figure 5.

Baseline characteristics of patients at risk of ≥ moderate DD were also significantly different among TR groups (Supplemental Table 4). Therefore, patients from each less-than-severe TR group were

TABLE 2 Baseline Characteristics of the Matched Cohort Across the Different Severities of Functional Tricuspid Regurgitation

	No FTR (n = 375)	Mild FTR (n = 375)	Moderate FTR (n = 375)	Severe FTR (n = 125)	*P* Value
Age, y	59.4 (48.1-67.7)	61.3 (48.8-70.0)	59.6 (46.0-70.3)	58.9 (46.8-71.0)	0.50
BMI, kg/m^2	27.2 (23.4-32.4)	27.4 (23.8-32.6)	26.8 (23.4-32.5)	26.5 (22.7-32.2)	0.65
Women	296 (79)	313 (83)	301 (80)	101 (81)	0.45
New-onset atrial fibrillation	45 (12)	44 (12)	42 (11)	13 (10)	0.96
Hypertension	145 (39)	157 (42)	142 (38)	45 (36)	0.58
Sleep apnea	58 (15)	69 (18)	70 (19)	19 (15)	0.56
Diabetes mellitus	87 (23)	84 (22)	71 (19)	24 (19)	0.45
Chronic lung disease	79 (21)	67 (18)	67 (18)	23 (18)	0.64
HFpEF	63 (17)	64 (17)	55 (15)	20 (16)	0.81
CAD	69 (18)	54 (14)	63 (17)	22 (18)	0.52

Values are n (%) or median (Q1-Q3).
Abbreviations as in Table 1.

matched in a 3:1 ratio to 34 at-risk patients (with no HFpEF or ≥ moderate DD at baseline) with severe FTR (Supplemental Table 5). Over median 2.9 years (Q1, Q3: 1.4-5.0 years), ≥ moderate DD developed in 10 of 102 patients with no FTR (2.7 per 100 person-years); 22 of 102 patients with mild FTR (6.0 per 100 person-years); 27 of 102 patients with moderate FTR (7.2 per 100 person-years), and 8 of 34 patients with severe FTR (9.2 per 100 person-years). Duration of follow-up was similar across all groups ($P > 0.41$). Mild (HR: 2.16 [95% CI: 1.02-4.56]; $P = 0.04$) and ≥ moderate FTR (HR: 2.82 [95% CI: 1.40-5.69]; $P = 0.004$) were associated with incident ≥ moderate DD vs no FTR (**Figure 1**, **Central Illustration**).

Similar results were observed in a sensitivity analysis involving a subset of matched patients without ≥ moderate RV enlargement or chronic lung disease (Supplemental Results). In another subset, matched patients with pulmonary vascular resistance >3 WU on invasive right heart catheterization (available in 165 of 1,250 patients; 108 patients with PVR >3 WU) and those without invasive catheterization but with RV systolic pressure >70 mm Hg and midsystolic or late-systolic notch in RV outflow tract pulsed-wave Doppler[28] (15 patients) were excluded (total 123 patients). Both ≥ moderate (11%, 16%, 24%, and 35% in no, mild, moderate, and severe TR; $P < 0.001$) and severe DD (2%, 5%, 8%, and 9%; $P < 0.001$) still occurred more frequently with increasing TR severity.

A sensitivity analysis examining prevalence and incidence of DD defined by ≥3 of 4 or ≥2 of 3 (if 1 variable was missing) abnormal diastolic function parameters was performed in the matched groups (Supplemental Results, Supplemental Figure 6).

The multivariable analysis of factors associated with incident DD pertaining to the overall (unmatched) cohort is present in **Table 5**. All other results pertinent to the overall cohort were included in the Supplemental Results (Supplemental Figure 7, Supplemental Tables 8 to 14).

INCIDENT TR AND DD. In patients with < moderate TR at baseline, ≥ moderate TR developed in 1,700 patients over median 3.1 years (Q1-Q3: 1.5-5.6 years). AF (persistent > paroxysmal > sinus rhythm) was associated with increased risk of incident TR (Supplemental Figure 8). Patients with DD at baseline developed ≥moderate TR significantly more often than patients without DD (**Figure 2**, **Central Illustration**), and the association remained despite adjustments to age, sex, and rhythm including persistent vs paroxysmal AF (HR of incident TR for ≥ moderate DD [vs no DD] was 1.96 [95% CI: 1.73-2.22]; HR for severe DD [vs no severe DD] was 2.22 [95% CI: 1.80-2.73]).

In patients with < moderate TR who did not have HFpEF or severe DD at baseline, the development of severe DD at follow-up was associated with increased risk of incident moderate/severe TR (age-, sex-, and rhythm-adjusted HR: 2.50 [95% CI: 1.83-3.42]; $P < 0.001$). Similarly, in patients with < moderate TR who did not have HFpEF or ≥ moderate DD at baseline, the development of ≥ moderate DD was associated with risk of incident moderate/severe TR (age-, sex-, and rhythm-adjusted HR: 1.97 [95% CI: 1.58-2.46]; $P < 0.001$).

CLINICAL OUTCOMES ACCORDING TO TR AND DD. Over median 5.0 years (Q1-Q3: 2.7-7.9 years), at least 1 HF hospitalization occurred in 453 of 30,428 patients and all-cause death in 4,323. Patients with concomitant ≥ moderate TR and DD at baseline had the highest rates of HF hospitalizations and mortality compared with patients with 1 or neither condition,

TABLE 3 Cardiac Structure and Function in the Matched Cohort Across the Different Severities of Functional Tricuspid Regurgitation

	n	No TR (n = 375)	Mild TR (n = 375)	Moderate TR (n = 375)	Severe TR (n = 125)	*P* Value
LVEDD, mm	1,045	46.0 (43.0-49.0)	45.0 (42.0-48.0)	45.0 (41.0-48.0)	40.0 (37.0-45.0)	<0.001
LVESD, mm	1,014	29.0 (26.0-32.0)	29.0 (26.0-32.0)	28.0 (25.0-31.0)	25.0 (22.5-29.0)	<0.001
EF, %	1,250	63.0 (60.0-67.0)	63.0 (60.0-66.0)	63.0 (59.0-67.0)	64.0 (60.0-68.0)	0.09
LV mass index, g/m^2	1,027	76.5 (68.0-90.0)	80.0 (67.5-92.5)	76.0 (64.0-91.0)	68.0 (58.0-80.0)	<0.001
Mitral medial E/e' ratio	1,013	8.9 (7.5-11.1)	10.0 (8.0-12.1)	10.0 (7.8-12.2)	10.0 (8.0-14.0)	0.001
Mitral lateral E/e' ratio	781	7.4 (5.8-10.0)	7.5 (6.0-10.0)	7.3 (5.7-10.0)	6.9 (5.0-10.0)	0.42
TR velocity, m/s	956	2.3 (2.1-2.5)	2.5 (2.3-2.8)	2.8 (2.5-3.4)	3.6 (2.7-4.2)	<0.001
RVSP, mm Hg	952	25.0 (23.0-30.0)	30.0 (26.0-38.0)	39.0 (31.0-56.0)	62.5 (42.2-82.0)	<0.001
LAVI, mL/m^2	971	25.0 (21.0-31.0)	27.0 (22.0-34.0)	28.0 (23.0-35.0)	26.0 (21.0-33.8)	<0.001
Medial mitral e', cm/s	1,030	8.0 (6.0-10.0)	8.0 (6.0-10.0)	8.0 (6.0-10.0)	6.5 (5.0-9.0)	<0.001
Medial mitral s', cm/s	569	8.0 (7.0-9.0)	7.5 (7.0-9.0)	7.0 (6.0-9.0)	7.0 (5.0-8.0)	<0.001
Lateral mitral e', cm/s	796	10.0 (8.0-13.0)	10.0 (8.0-12.0)	10.0 (8.0-13.0)	10.0 (8.0-12.0)	0.42
Lateral mitral s', cm/s	557	9.0 (7.0-10.0)	8.5 (7.3-10.0)	8.0 (7.0-10.0)	9.0 (7.0-10.0)	0.57
Mild MR	1,250	43 (11)	122 (33)	142 (38)	43 (34)	<0.001
Any RV enlargement	810	–	208 (63)	262 (71)	101 (92)	<0.001
RV end-diastolic area, cm^2	810	–	22.7 (19.7-26.6)	21.9 (17.3-28.2)	31.0 (24.8-36.9)	<0.001
RV end-systolic area, cm^2	810	–	12.6 (10.6-15.3)	12.3 (9.7-17.8)	22.0 (15.0-27.9)	<0.001
RA enlargement	798	–	72 (19)	105 (33)	87 (80)	<0.001
RA end-systolic volume, mL	798	–	41.9 (29.8-55.4)	50.5 (34.8-73.1)	57.3 (68.2-120.1)	<0.001
RV FAC, %	810	–	44.1 (39.1-48.5)	41.6 (31.1-48.3)	27.1 (20.8-38.4)	<0.001
LA reservoir strain, %	776	–	27.4 (21.4-34.7)	24.4 (17.8-31.6)	19.8 (14.0-26.6)	<0.001
LA reservoir strain <24%	776	–	118 (35)	157 (48)	75 (69)	<0.001
RA reservoir strain, %	730	–	32.1 (23.5-40.5)	28.1 (18.2-34.9)	17.7 (11.4-26.4)	<0.001
RA reservoir strain <19.8%	730	–	52 (16)	87 (29)	61 (55)	<0.001
Severe DD	1,006[a]					<0.001
No		302 (81)	286 (76)	260 (69)	79 (63)	
Unknown		66 (18)	68 (18)	80 (21)	30 (24)	
Yes		7 (2)	21 (6)	35 (9)	16 (13)	
≥ Moderate DD	953[a]					<0.001
No		230 (61)	227 (61)	185 (49)	39 (31)	
Unknown		104 (28)	81 (22)	86 (23)	26 (21)	
Yes		41 (11)	67 (18)	104 (28)	60 (48)	
HFpEF probability using H2FPEF score, %	876	29.7 (12.2-60.9)	45.5 (22.8-78.9)	61.4 (31.6-88.8)	88.7 (58.4-96.8)	<0.001
HFA-PEFF risk categories	1,250					<0.001
Low		196 (52)	143 (38)	109 (29)	17 (14)	
Intermediate		171 (46)	205 (55)	204 (54)	54 (43)	
High		8 (2)	27 (7)	27 (7)	54 (43)	

Values are n (%) and median (Q1-Q3). [a]Number of unknowns is not included.

DD = diastolic dysfunction; EF = ejection fraction; LAVI = left atrial volume index; LV = left ventricle; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; MR = mitral regurgitation; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation.

whether considering severe or ≥ moderate DD (Figure 3). Conversely, patients with ≥ moderate TR and no ≥ moderate DD at baseline had mortality rates similar to patients with < moderate TR and no ≥ moderate DD. On the other hand, the presence of ≥ moderate DD was invariably associated with increased mortality rate, with the concomitant presence of ≥ moderate TR conferring additional mortality; this association remained at the multivariable level (Supplemental Tables 6 and 7).

INTEROBSERVER VARIABILITY IN RV AND RA MEASUREMENTS. In a 10-patient sample randomly selected for measurement by different observers, intraclass correlation coefficient showed good reliability (0.77 for RV end-diastolic area; 0.85 for RV end-systolic area; 0.75 for RA volume; 0.73 for RA strain; 0.84 for LA strain).

DISCUSSION

This study evaluated the prevalence, incidence, and outcomes of DD across severities of FTR in the absence of other structural heart disease. DD was more common with increasing FTR severity, independent of clinical characteristics, as was biatrial dysfunction evidenced by impaired LA and RA strain.

Furthermore, in patients without known HF or apparent DD at baseline, incident DD developed more frequently in patients with higher severity of FTR. These findings were confirmed in the subset of patients without lung disease or RV enlargement. The presence of DD and AF were associated with development of ≥ moderate TR at follow-up. Importantly, the association between ≥ moderate TR and worse clinical outcomes was drastically diminished in the absence of DD, whereas the presence of DD was invariably associated with worse outcomes, with the concomitant presence of ≥ moderate TR conferring additional mortality. Our data indicate that idiopathic FTR is highly associated with LV DD, whether clinically apparent or not at baseline, with important prognostic implications.

TABLE 4 Association of Different Severities of Tricuspid Regurgitation With Prevalent ≥ Moderate and Severe Diastolic Dysfunction in the Matched Cohort

	OR (95% CI)	*P* Value
Prevalent ≥ moderate DD		
Mild FTR (vs no FTR)	1.66 (1.08-2.54)	0.02
Moderate FTR (vs no FTR)	3.15 (2.10-4.75)	<0.001[a]
Severe FTR (vs no FTR)	8.63 (5.12-14.55)	<0.001[a,b]
Prevalent severe DD		
Mild FTR (vs no FTR)	3.17 (1.33-7.57)	0.009
Moderate FTR (vs no FTR)	5.81 (2.54-13.29)	<0.001[a]
Severe FTR (vs no FTR)	8.74 (3.47-21.97)	<0.001[a]

ORs were assessed using binary logistic regression model for present vs absent diastolic dysfunction (DD) (unknown was not considered in this analysis). [a]$P < 0.05$ compared with mild functional tricuspid regurgitation (FTR). [b]$P < 0.05$ compared with moderate FTR.

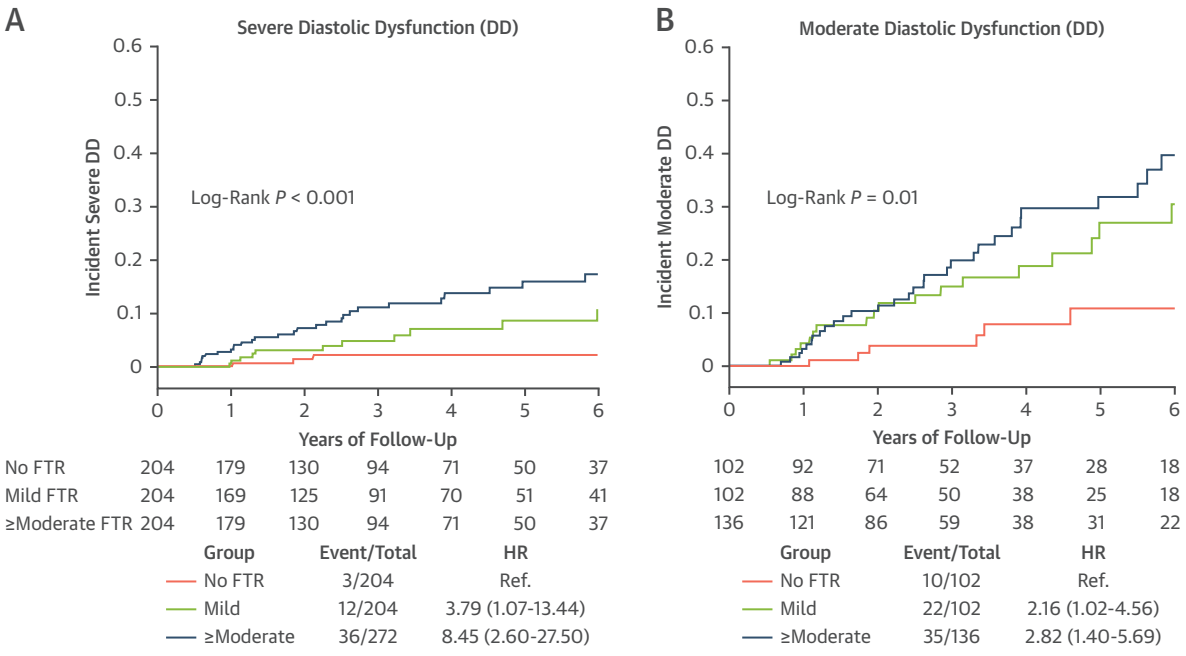
PATHOPHYSIOLOGY OF TR IN HFpEF. TR develops in DD or HFpEF by multiple mechanisms.[3,4,29] First, the associated postcapillary PH results in RV remodeling, with subsequent tricuspid annulus dilation and leaflet tethering causing ventricular FTR. Second, systemic inflammation can cause coronary microvascular dysfunction and myocardial structural changes[16-18] that directly affect the RA resulting in atrial fibrosis, remodeling, dilation, and AF, which in turn worsen atrial remodeling and myopathy, leading to worsening atrial TR.[19] Indeed, with increasing TR severity at baseline, an increasing proportion of patients had impaired LA and RA strain, indicating greater burden of biatrial myopathy, which is common in HFpEF and is associated with more adverse hemodynamic signatures and poorer outcomes.[30] Among patients with normal EF presenting with dyspnea, an LA strain <24.5% is 94% specific for HFpEF[31] and the prevalence of abnormal LA strain (<24%) increased from 35% to 48% to 69% with increasing TR severity, providing further evidence for high burden of DD and potentially occult HFpEF in patients with apparently isolated TR. A strong association has been described between AF and HFpEF as a result.[32] Therefore, DD can precede, and predispose to, TR via the first mechanism, or DD and TR may both be concomitant parallel manifestations of shared myocardial insults. Although severe TR with significant RV enlargement can result in diastolic ventricular interaction and elevated LV filling pressures in the absence of left heart disease,[33,34] the association between prevalent DD and TR severity remained in a sensitivity analysis excluding patients with RV enlargement, further supporting the association between DD and TR.

Although many patients with TR are clinically diagnosed as having symptomatic valve disease, the majority also fulfil diagnostic criteria for HFpEF. Lurz et al[35] observed a mean LA pressure of 20 mm Hg, mean EF 51%, and median NT-proBNP of 3,110 pg/mL among patients with severe TR. Indeed, both DD at baseline and AF were associated with incident significant TR in this study, and strategies addressing both (SGLT2 inhibitors, rhythm control) may be effective in preventing TR.

PREVALENCE OF DD IN PATIENTS WITH SECONDARY TR. The prevalence of DD showed a graded increase with increasing TR severity, independent of clinical characteristics, including incident AF, suggesting that patients with idiopathic FTR frequently have underlying primary left heart disease that can contribute to the development or progression of TR. The observed increase in HFpEF probability and decrease in LA and RA strain with increasing FTR severity further support the potential for a large burden of undiagnosed HFpEF in patients with FTR.

In patients with severe isolated TR, symptoms of peripheral edema, ascites, and painful hepatomegaly can be explained by the severe TR itself and the associated RV failure.[36] Symptoms of exertional dyspnea and fatigue are often perceived to indicate a low cardiac output state caused by ventricular interaction and TR, but can also be caused by concomitant, potentially undiagnosed HFpEF. In patients with symptomatic severe TR enrolled in the TRILUMINATE (The Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal) randomized clinical trial, two-thirds of patients who underwent percutaneous tricuspid transcatheter edge-to-edge repair were still in NYHA functional class II or III at 1-year follow-up, despite the reduction of TR to ≤ moderate in 89%,[37] and there was minimal improvement in the 6-minute walk distance. These observations in addition to the neutral impact of percutaneous tricuspid intervention on

FIGURE 1 **Incident Severe and ≥ Moderate DD According to TR Severity in the Matched Cohort**



Risk of incident severe diastolic dysfunction (DD) (A) and ≥ moderate DD (B) was greater with increasing tricuspid regurgitation severity. HR and 95% CI are shown. Because there are fewer patients with severe DD at index evaluation than those with moderate DD or severe DD, the number at risk for severe DD is higher than the number at risk for moderate or severe DD. FTR = functional tricuspid regurgitation; Ref. = Reference.

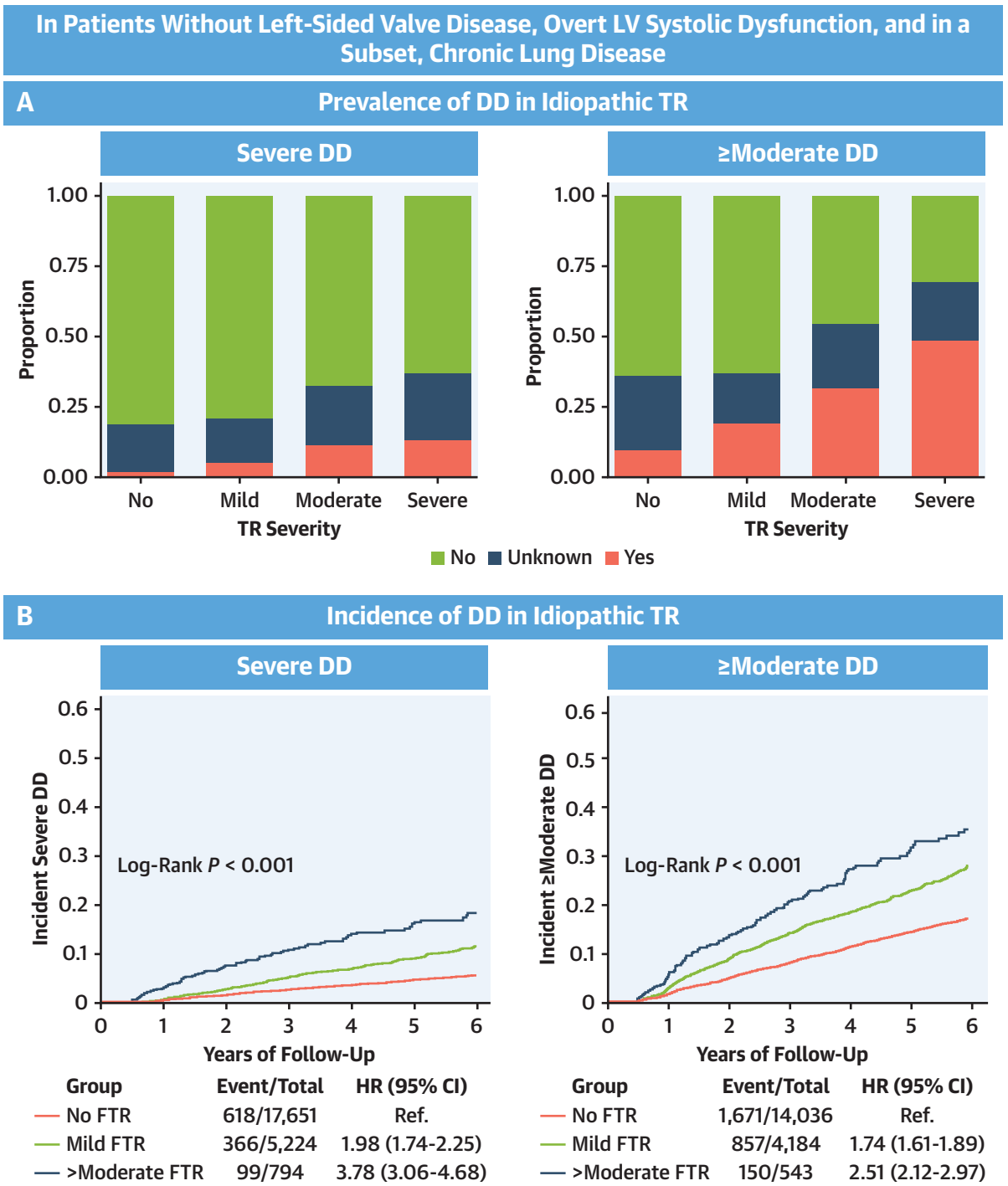
mortality and rates of HF hospitalization raise the possibility of undiagnosed HFpEF, with TR being secondary rather than primarily causal. Mild and moderate TR are considered insufficient to cause symptoms on their own, meaning that the presence of exertional dyspnea in these patients in the absence of clear etiology should raise the suspicion for underlying HFpEF.[36] Even in the absence of symptoms, the presence of DD in patients with FTR and no identified cause can indicate an early-stage or "preclinical" HFpEF that requires follow-up for the development of clinical HFpEF.

INCIDENT DD IN PATIENTS WITH SECONDARY TR. Patients with ≥ moderate FTR without HF or DD apparent at baseline developed DD more frequently compared with patients without FTR. These findings indicate that idiopathic FTR either heralds a high risk of progression to DD or indicates that DD is in fact present at the index evaluation, but may not be overtly evident by conventional echo-Doppler measures, which are known to be insensitive to earlier stages of DD.[38] From this perspective, the presence of TR may be considered a clue to occult DD.

CLINICAL OUTCOMES ACCORDING TO TR AND DD. Isolated TR has been associated with increased risk for mortality and HF hospitalizations.[11-13] We show that the presence of DD was an important determinant of both outcomes in patients with TR. The association between ≥ moderate TR and either HF hospitalizations or mortality was significantly reduced in the absence of DD, reaching null for mortality. On the other hand, the concomitant presence of ≥ moderate TR and DD had a synergistic association with worse clinical outcomes. The presence of TR in these patients likely indicates more advanced DD. These observations highlight the importance of identifying patients with TR who have DD who may benefit from close follow-up and preventive or therapeutic interventions directed toward HFpEF.

STUDY LIMITATIONS. This is a retrospective study that included patients at a tertiary referral center with potential referral bias. All patients were required to have a follow-up TTE, which was based on a clinical indication. Given the retrospective and nonstandardized nature of the study, it is anticipated that patients with more severe TR would have a closer

CENTRAL ILLUSTRATION **Prevalence, Incidence, and Outcomes of Diastolic Dysfunction in Idiopathic Tricuspid Regurgitation and Relation of Diastolic Dysfunction to Incident Tricuspid Regurgitation**



Naser JA, et al. JACC Cardiovasc Imaging. 2024;■(■):■-■.

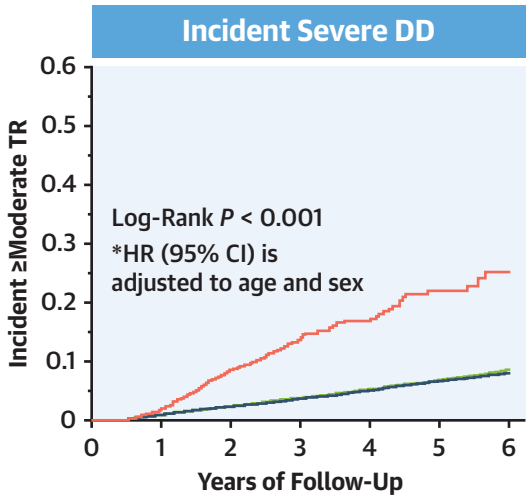
Analysis included here reflects the overall cohort. (A) Prevalence of diastolic dysfunction (DD) with different severities of functional idiopathic tricuspid regurgitation (TR). (B) Incidence of DD according to TR severity. (C) Incident ≥ moderate TR according to DD status. (D) All-cause mortality rates according to TR and DD status. FTR = functional tricuspid regurgitation; LV = left ventricular; MDD = moderate diastolic dysfunction; SDD = severe diastolic dysfunction.

Continued on the next page

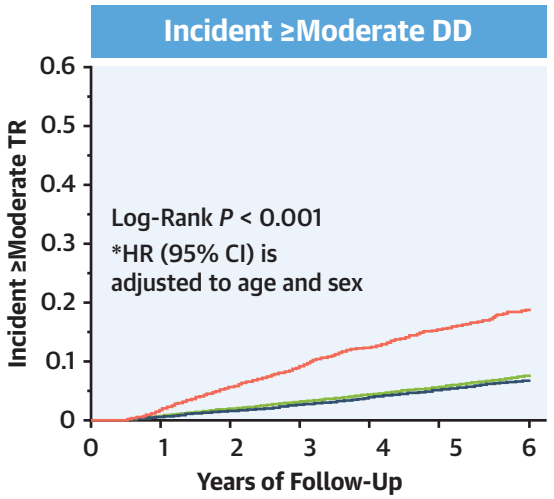
CENTRAL ILLUSTRATION ■■■

In Patients Without Left-Sided Valve Disease, Overt LV Systolic Dysfunction, and in a Subset, Chronic Lung Disease

C Incident ≥Moderate TR According to DD

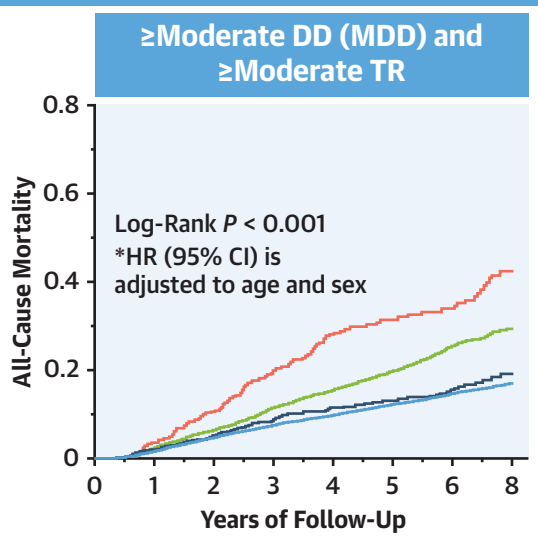


Severe DD	Event/Total	HR (95% CI)*
Yes	102/690	2.58 (2.10-3.16)
No	1,286/23,618	Ref.
Unknown	312/4,840	0.91 (0.80-1.05)

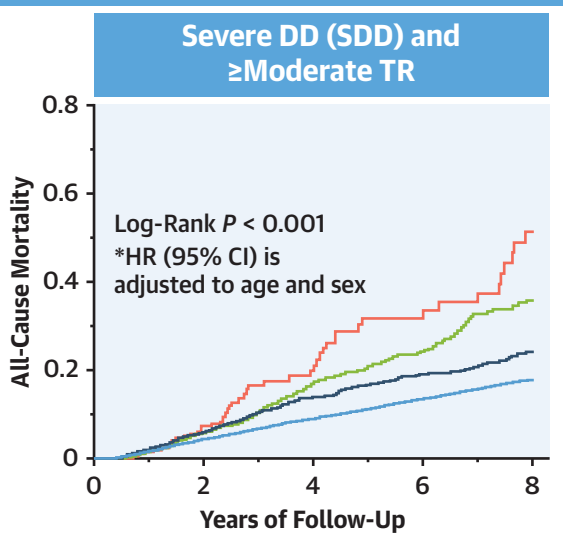


Moderate DD	Event/Total	HR (95% CI)*
Yes	383/3,273	2.14 (1.89-2.43)
No	955/18,689	Ref.
Unknown	362/7,186	0.83 (0.74-0.95)

D All-Cause Mortality According to TR and DD



Group	Event/Total	HR (95% CI)*
+MDD & +TR	116/418	2.21 (1.83-2.67)
+MDD & −TR	630/3,273	1.38 (1.25-1.51)
−MDD & +TR	81/575	1.06 (0.84-1.32)
−MDD & −TR	2,256/18,689	Ref.



Group	Event/Total	HR (95% CI)*
+SDD & +TR	45/144	2.26 (1.68-3.04)
+SDD & −TR	156/690	1.56 (1.32-1.83)
−SDD & +TR	150/866	1.26 (1.07-1.49)
−SDD & −TR	3,080/23,618	Ref.

Naser JA, et al. JACC Cardiovasc Imaging. 2024;■(■):■-■.

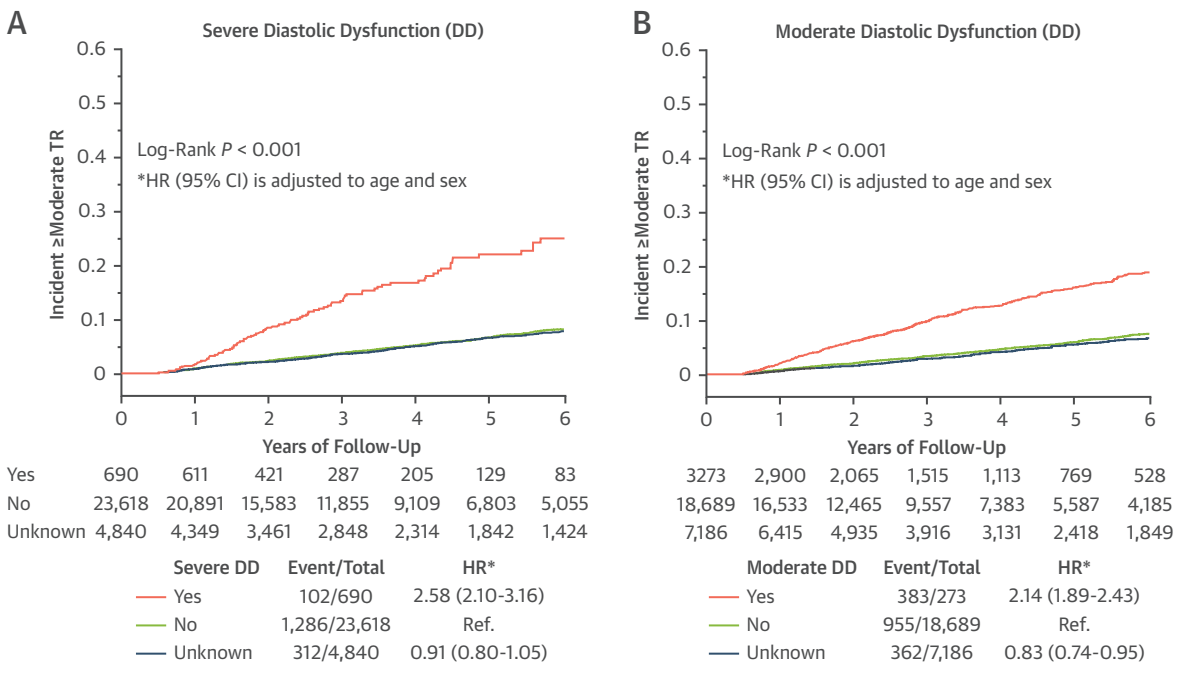
TABLE 5 Multivariable Risk Factors Associated With Incident Severe and ≥ Moderate Diastolic Dysfunction in the Overall Cohort

	HR (95% CI)	*P* Value
Severe diastolic dysfunction		
Age, y[a]	1.05 (1.04-1.05)	<0.001
BMI, kg/m^2[a]	1.03 (1.02-1.04)	<0.001
Atrial fibrillation	2.21 (1.86-2.62)	<0.001
Hypertension	1.25 (1.09-1.43)	0.002
Diabetes mellitus	1.27 (1.11-1.45)	<0.001
FTR		<0.001
Mild (vs no FTR)	1.57 (1.37-1.79)	<0.001
≥ Moderate (vs no FTR)	2.51 (2.01-3.13)	<0.001
≥ Moderate diastolic dysfunction		
Age, y[a]	1.04 (1.04-1.05)	<0.001
BMI, kg/m^2[a]	1.02 (1.02-1.03)	<0.001
Atrial fibrillation	1.76 (1.54-2.00)	<0.001
Hypertension	1.23 (1.13-1.33)	<0.001
Chronic lung disease	1.13 (1.004-1.27)	0.04
FTR		<0.001
Mild (vs no FTR)	1.41 (1.30-1.54)	<0.001
≥ Moderate (vs no FTR)	1.71 (1.44-2.03)	<0.001

[a]HR is presented per unit change.
Abbreviations as in Table 1.

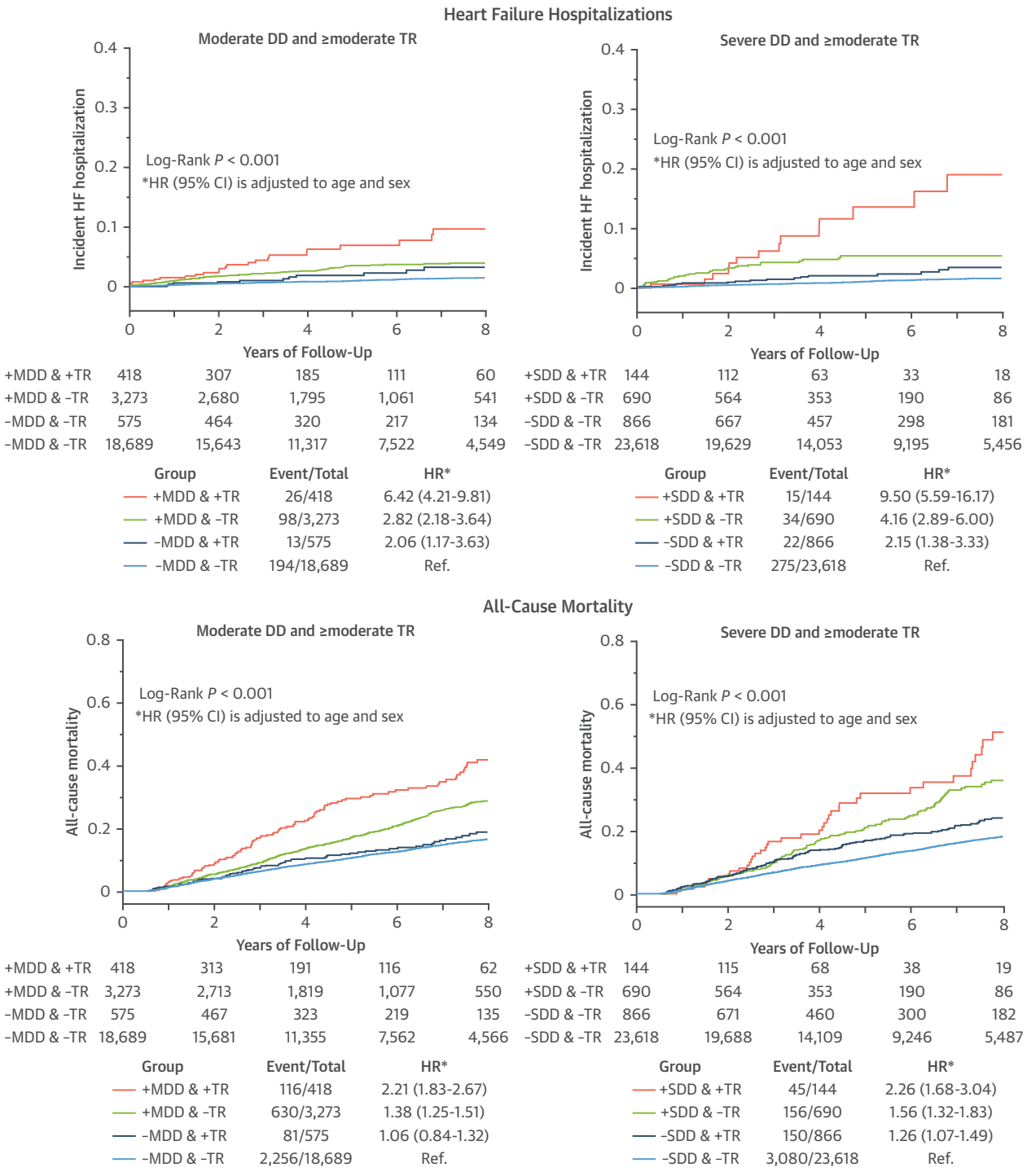
follow-up. However, follow-up time was similar in the matched cohort across the severities of TR, minimizing the impact of this issue. Patients with severe FTR were younger with less comorbidities, likely caused by a survival bias in these patients over older, multimorbid patients. In the setting of severe TR, Doppler echocardiography can underestimate the severity of PH.[21,39] Without concurrent invasive hemodynamics, PH could not be classified into postcapillary vs precapillary. Nonetheless, the exclusion of patients with significant left valve disease, LV systolic dysfunction, connective tissue disease, congenital heart disease, pacemakers, and in a subanalysis, primary lung disease, significantly narrows down possible underlying etiologies. HFpEF at baseline was defined using ICD codes for HF and the absence of current/previous low EF, because manual chart review for undocumented HFpEF was not feasible for this large cohort, and chart review would not have been adequately sensitive given the variability in clinical recognition and documentation of signs and symptoms of HF. Indeed, the insensitivity of ICD definitions of HF is an important implication of this study, and the presence of TR can be taken as a

FIGURE 2 Incidence of ≥ Moderate TR at Follow-Up in Patients With and Without DD



Incident ≥ moderate tricuspid regurgitation (TR) occurred more commonly in patients with severe diastolic dysfunction (DD) (A) or ≥ moderate DD (B).

FIGURE 3 Rates of HF Hospitalizations and All-Cause Mortality According to TR and DD Status at Baseline



HF = heart failure; MDD = moderate diastolic dysfunction; SDD = severe diastolic dysfunction; other abbreviations as in Figures 1 and 2.

clue to pursue to the diagnosis. HF hospitalizations were assessed based upon primary admission diagnosis in our medical system, a method that may be inadequately sensitive, and HF admissions at other facilities would not be captured with this method. Although this leads to underestimation of the true incidence of HF hospitalization, this does not affect the veracity of our comparative results, because this limitation applies equally to all patients.

For simplicity, we defined ≥ moderate and severe DD by the presence of ≥2 and ≥3 abnormal DD parameters, respectively. We acknowledge, however, that the number of abnormal DD parameters does not necessarily reflect the severity of DD. Current guidelines recommend the presence of ≥3 abnormal parameters to define DD, which constituted "severe DD" in our study. The presence of 2 abnormal parameters is considered indeterminate, requiring additional parameters.[21] However, these parameters were not obtained routinely, and although specific, the sensitivity of the guideline definition of DD is modest.[38] Therefore, we used ≥2 abnormal diastolic parameters to indicate ≥moderate DD.

CONCLUSIONS

In a population without chronic AF, significant left-sided valve disease, LV systolic dysfunction, connective tissue disease, cardiac device, or primary lung disease, secondary TR was independently associated with prevalent DD, increasing probability of underlying HFpEF, and a greater risk for developing clinically overt DD. The concomitant presence of TR and DD conferred significant morbidity and mortality, whereas the association between TR and worse outcomes was drastically diminished in the absence of DD. These data indicate the need to consider left heart disease and HFpEF in patients with FTR of unclear etiology who have exertional symptoms, and they suggest that even in patients with TR without overt HFpEF, strategies and therapies to prevent progression to clinical HFpEF may be of value.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients without significant left-sided valve disease, overt LV systolic dysfunction, other structural heart disease, connective tissue disease, or known lung disease, secondary TR was independently associated with prevalent DD and increasing HFpEF probability score. The incidence of newly recognized DD was significantly higher at follow-up in patients with secondary TR and increased with increasing TR severity. Patients with ≥ moderate TR and DD had the greatest risk of worse outcomes, whereas the association between TR and adverse outcomes was significantly diminished in the absence of DD.

TRANSLATIONAL OUTLOOK: Patients with secondary TR of undefined etiology who have exertional dyspnea or fatigue should be evaluated appropriately for underlying HFpEF and receive appropriate therapy if diagnosed. Patients with secondary TR of undefined etiology without clear evidence of DD on resting echocardiography may have subclinical DD and are at increased risk of developing more clinically overt DD at follow-up. Patients with FTR and DD display worse outcomes and may benefit from therapeutic strategies direct at DD.

REFERENCES

1. Fan Y, Pui-Wai Lee A. Valvular disease and heart failure with preserved ejection fraction. *Heart Fail Clin*. 2021;17(3):387–395.

2. Ren QW, Li XL, Fang J, et al. The prevalence, predictors, and prognosis of tricuspid regurgitation in stage B and C heart failure with preserved ejection fraction. *ESC Heart Fail*. 2020;7(6):4051–4060.

3. Obokata M, Reddy YNV, Melenovsky V, et al. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J*. 2019;40(8):689–697.

4. Harada T, Obokata M, Omote K, et al. Functional tricuspid regurgitation and right atrial remodeling in heart failure with preserved ejection fraction. *Am J Cardiol*. 2022;162:129–135.

5. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging*. 2019;12(3):433–442.

6. Galloo X, Dietz MF, Fortuni F, et al. Prognostic implications of atrial vs. ventricular functional

tricuspid regurgitation. *Eur Heart J Cardiovasc Imaging*. 2023;24(6):733-741.

7. Topilsky Y, Khanna A, Le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging*. 2012;5(3):314-323.

8. Hahn RT. Tricuspid Regurgitation. *N Engl J Med*. 2023;388(20):1876-1891.

9. Utsunomiya H, Itabashi Y, Mihara H, et al. Functional tricuspid regurgitation caused by chronic atrial fibrillation: a real-time 3-dimensional transesophageal echocardiography study. *Circ Cardiovasc Imaging*. 2017;10(1):e004897.

10. Fender EA, Petrescu I, Ionescu F, et al. Prognostic importance and predictors of survival in isolated tricuspid regurgitation: a growing problem. *Mayo Clin Proc*. 2019;94(10):2032-2039.

11. Topilsky Y, Nkomo VT, Vatury O, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging*. 2014;7(12):1185-1194.

12. Abe Y, Akamatsu K, Ito K, et al. Prevalence and prognostic significance of functional mitral and tricuspid regurgitation despite preserved left ventricular ejection fraction in atrial fibrillation patients. *Circ J*. 2018;82(5):1451-1458.

13. Patlolla SH, Schaff HV, Nishimura RA, et al. Incidence and burden of tricuspid regurgitation in patients with atrial fibrillation. *J Am Coll Cardiol*. 2022;80(24):2289-2298.

14. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. *JAMA*. 2023;329(10):827-838.

15. Borlaug BA, Sharma K, Shah SJ, et al. Heart failure with preserved ejection fraction: JACC scientific statement. *J Am Coll Cardiol*. 2023;81(18):1810-1834.

16. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62(4):263-271.

17. Westermann D, Lindner D, Kasner M, et al. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. *Circ Heart Fail*. 2011;4(1):44-52.

18. Mohammed SF, Hussain S, Mirzoyev SA, et al. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation*. 2015;131(6):550-559.

19. Bisbal F, Baranchuk A, Braunwald E, et al. Atrial failure as a clinical entity: JACC review topic of the week. *J Am Coll Cardiol*. 2020;75(2):222-232.

20. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32(1):1-64.

21. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.

22. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14.

23. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30(4):303-371.

24. Hahn RT, Lawlor MK, Davidson CJ, et al. Tricuspid valve Academic Research Consortium definitions for tricuspid regurgitation and trial endpoints. *Eur Heart J*. 2023;44(43):4508-4532.

25. Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;138(9):861-870.

26. Reddy YNV, Kaye DM, Handoko ML, et al. Diagnosis of heart failure with preserved ejection fraction among patients with unexplained dyspnea. *JAMA Cardiol*. 2022;7(9):891-899.

27. Pieske B, Tschope C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40(40):3297-3317.

28. Arkles JS, Opotowsky AR, Ojeda J, et al. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. *Am J Respir Crit Care Med*. 2011;183(2):268-276.

29. Hahn RT, Badano LP, Bartko PE, et al. Tricuspid regurgitation: recent advances in understanding pathophysiology, severity grading and outcome. *Eur Heart J Cardiovasc Imaging*. 2022;23(7):913-929.

30. Omote K, Sorimachi H, Obokata M, et al. Biatrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2024;26(2):288-298.

31. Reddy YNV, Obokata M, Egbe A, et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;21(7):891-900.

32. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133(5):484-492.

33. Andersen MJ, Nishimura RA, Borlaug BA. The hemodynamic basis of exercise intolerance in tricuspid regurgitation. *Circ Heart Fail*. 2014;7(6):911-917.

34. Baratto C, Caravita S, Corbetta G, et al. Impact of severe secondary tricuspid regurgitation on rest and exercise hemodynamics of patients with heart failure and a preserved left ventricular ejection fraction. *Front Cardiovasc Med*. 2023;10:1061118.

35. Lurz P, Orban M, Besler C, et al. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. *Eur Heart J*. 2020;41(29):2785-2795.

36. Arsalan M, Walther T, Smith RL 2nd, et al. Tricuspid regurgitation diagnosis and treatment. *Eur Heart J*. 2017;38(9):634-638.

37. Sorajja P, Whisenant B, Hamid N, et al. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med*. 2023;388(20):1833-1842.

38. Obokata M, Kane GC, Reddy YN, et al. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation*. 2017;135(9):825-838.

39. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561-632.

KEY WORDS diastolic function, echocardiography, functional regurgitation, heart failure, HFpEF, tricuspid regurgitation, valve disease

APPENDIX For expanded Methods and Results sections, as well as supplemental figures and tables, please see the online version of this paper.