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Tricuspid Regurgitation Across the Spectrum of Heart Failure With Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Secondary tricuspid regurgitation (STR) in heart failure with preserved ejection fraction (HFpEF) is linked to more advanced stages with pulmonary vascular disease (PVD), but it may also develop at earlier stages of HFpEF, such as those with isolated exercise-induced congestion.

OBJECTIVES This study sought to evaluate the prevalence, distribution, and prognostic significance of STR mechanisms across the spectrum of HFpEF.

METHODS Cardiac structure, function, hemodynamics, and clinical outcomes were compared among patients with HFpEF phenotypes categorized according to the presence of PVD (pulmonary vascular resistance >2 WU), and elevation in filling pressure at rest vs provocation (leg-elevation or exercise), as well as according to the presence of atrial or ventricular STR (A-STR, V-STR).

RESULTS Of 1,091 patients (median age 65 years, 60.3% women), 669 (61.3%) had HFpEF (20.2% exercise HFpEF − PVD, 38.6% rest HFpEF − PVD, 15.5% exercise HFpEF + PVD, 25.7% rest HFpEF + PVD). Moderate or severe STR was present in 17.4% overall, but increased with PVD (6.7%, 11.6%, 18.3%, and 33.7%, respectively), although moderate or severe STR was still more common in exercise-only HFpEF vs noncardiac dyspnea patients (11.7% vs 6.5%; $P = 0.047$). Most STR (69%) fulfilled criteria for V-STR, but those individuals had similar atrial fibrillation prevalence and greater atrial remodeling compared with A-STR. V-STR was independently associated with composite of death or heart failure (HF) hospitalization (multivariable HR: 1.70; 95% CI: 1.10-2.65) as well as death and HF hospitalizations each alone, whereas A-STR was associated with increased risk of HF hospitalizations (multivariable Fine-Gray HR: 2.21; 95% CI: 1.12-4.37).

CONCLUSIONS STR in HFpEF is associated with PVD and less strongly with higher resting filling pressure. Although V-STR is the more common phenotype of STR in HFpEF, these patients also have substantial atrial myopathy, suggesting a mixed mechanism. TR was more prevalent in exercise HFpEF and exercise pulmonary hypertension than with noncardiac dyspnea; with none in the latter group having moderate-severe or severe TR, highlighting the importance of exercise hemodynamics. V-STR conferred excess mortality and HF hospitalizations, but A-STR conferred only excess HF hospitalizations. (JACC. 2025;86:2495-2508) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

A-STR = atrial secondary tricuspid regurgitation

BMI = body mass index

HFpEF = heart failure with preserved ejection fraction

mPAP = mean pulmonary artery pressure

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PAWP = pulmonary artery wedge pressure

PH = pulmonary hypertension

PVD = pulmonary vascular disease

PVR = pulmonary vascular resistance

RA = right atrial

RHC = right heart catheterization

RV = right ventricular

RV-FAC = right ventricular fractional area change

STR = secondary tricuspid regurgitation

TR = tricuspid regurgitation

V-STR = ventricular secondary tricuspid regurgitation

Secondary tricuspid regurgitation (STR) can develop in the setting of many cardiopulmonary diseases,[1-3] including heart failure with preserved ejection fraction (HFpEF).[4-6] HFpEF is frequently overlooked in patients with STR[7-11] and often mislabeled as idiopathic or isolated.[12,13] The spectrum of HFpEF spans patients with elevation in filling pressure exclusively during exercise to those with congestion apparent at rest,[14,15] and there are also patients with coexisting pulmonary vascular disease (PVD),[16] which may lead to right ventricular (RV) dysfunction.[5,16] STR in HFpEF can develop in the setting of RV dysfunction and PVD,[5] but recent evidence suggests that STR may also develop in earlier stages or phenotypes of HFpEF,[12,13] even in the absence of RV dysfunction. Data on the prevalence and characteristics of STR across the spectrum of HFpEF remain limited.

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STR is classified as atrial (A-STR) when right atrial (RA) remodeling results in tricuspid annular dilation and tricuspid regurgitation (TR), and ventricular (V-STR) when TR occurs because of RV remodeling and subsequent tricuspid leaflet tethering and annular dilation.[1,17,18] A-STR is more commonly linked with HFpEF, but the distribution and prognostic implications of this classification in HFpEF are not well established. The prespecified aims of the present study were to: 1) evaluate the prevalence of ≥moderate TR across the different phenotypes of HFpEF, classified according to the presence or absence of PVD, and the presence of rest vs exercise-induced elevation in PAWP, and across other groups of pulmonary hypertension (PH) and patients with noncardiac dyspnea; 2) evaluate and characterize the mechanism of ≥moderate TR (ie, A-STR vs V-STR) in patients with HFpEF; and 3) evaluate the prognostic impact of the different mechanisms of ≥moderate TR in HFpEF.

METHODS

STUDY POPULATION. The study was approved by the Mayo Clinic Institutional Review Board, who waived the requirement of informed consent. Following Minnesota state law, we excluded patients who denied authorization for their data to be used for research. Adult patients who underwent right heart catheterization (RHC) both at rest and during exercise at Mayo Clinic sites from February 2006 to June 2023 and who had a transthoracic echocardiogram from within 90 days before the RHC were identified retrospectively. When multiple transthoracic echocardiograms were available, the closest to the RHC procedure was examined. Exclusion criteria included previous cardiac surgery, cardiac implantable electronic device, low current or previous ejection fraction <50%, ≥moderate aortic valve regurgitation or stenosis, ≥moderate mitral regurgitation, any mitral stenosis, primary tricuspid valve disease (eg, rheumatic disease, carcinoid disease, tricuspid valve flail or prolapse, endocarditis), congenital heart disease, infiltrative/inflammatory/hypertrophic cardiomyopathy, and pericardial disease. Comorbidities were obtained according to International Classification of Diseases codes. In the case of atrial fibrillation (AF), electrocardiograms were also examined.

ECHOCARDIOGRAPHY. All transthoracic echocardiograms were performed in routine clinical practice by professional sonographers according to guidelines,[19] and interpreted by level III board-certified echocardiologists. The severity of TR was classified as none/trivial, mild, moderate, and moderate-severe/severe using an integrative approach based on color flow Doppler, density and shape of the regurgitant jet, proximal isovelocity surface area (effective regurgitant orifice area and regurgitant volume, as available), inferior vena cava size, and hepatic vein flow pattern, according to guidelines (Supplemental Appendix 1).[20] Subsets of 25 randomly selected patients from each TR severity grade (no, mild, moderate, moderate-severe/severe), for a total of 100 patients, were reviewed de novo to confirm TR severity and assess agreement. RV midventricular diameter at end-diastole as well as RV end-systolic and end-diastolic areas were measured in the RV-focused apical 4-chamber view, and the RV fractional area change (RV-FAC) was calculated.[21] RA end-systolic area and volume were measured from the apical 4-chamber view; the RA volume was measured by means of the single-plane summation method. Tricuspid valve tenting height was measured at end-systole as the distance between the tricuspid annulus plane and the atrial aspect of the leaflets. These measurements were performed by 4 readers (J.A.N., T.H., A.T., and C.K.W.). Interobserver agreement for measurements was assessed by means of the intraclass correlation coefficient (ICC) in a random 10-patient sample.

CLASSIFICATION OF STR. In accordance with current recommendations, STR was classified as V-STR when 1 or more of the following 5 criteria were met:

TABLE 1 Baseline Characteristics Among Patients With and Without HFpEF

	Phenotypes of HFpEF					No HFpEF				
	Rest HFpEF + PVD (n = 172)	Exercise HFpEF + PVD (n = 104)	Rest HFpEF − PVD (n = 258)	Exercise HFpEF − PVD (n = 135)	*P* Value[a]	Precapillary PH (n = 135)	Unclassified PH (n = 28)	Exercise PH Without HFpEF (n = 90)	Noncardiac Dyspnea (n = 169)	*P* Value[b]
Age, y	70 (64-76)	68 (63-73)	64 (55-70)	67 (59-72)	<0.01	64 (56-72)	54 (39-66)	68 (61-76)	53 (46-63)	<0.01
Female	115 (66.9)	72 (69.2)	133 (51.6)	69 (51.1)	<0.01	88 (65.2)	16 (57.1)	56 (62.2)	109 (64.5)	<0.01
BMI, kg/m^2	33.2 (27.9-38.0)	31.6 (26.7-36.2)	35.4 (29.4-40.5)	31.1 (27.0-35.0)	<0.01	30.2 (26.0-34.9)	30.2 (26.1-34.9)	28.0 (23.6-31.0)	28.3 (24.7-31.7)	<0.01
Chronic kidney disease	27 (15.7)	7 (6.8)	34 (13.2)	8 (5.9)	0.11	14 (10.3)	2 (6.7)	8 (9.0)	8 (4.8)	0.01
Diabetes mellitus	45 (26.2)	20 (19.2)	70 (27.1)	24 (17.8)	0.69	20 (14.8)	5 (17.9)	21 (23.3)	23 (13.6)	<0.01
Hypertension	75 (43.6)	50 (48.1)	129 (50.0)	62 (45.9)	0.32	52 (38.5)	9 (32.1)	45 (50.0)	44 (26.0)	<0.01
Sleep apnea	47 (27.3)	34 (32.7)	89 (34.5)	37 (27.4)	0.44	41 (30.4)	8 (28.6)	22 (24.4)	29 (17.2)	0.02
Ischemic stroke	10 (5.8)	2 (1.9)	10 (3.9)	5 (3.7)	<0.01	7 (5.2)	0 (0.0)	6 (6.7)	2 (1.2)	0.20
Atrial fibrillation	67 (39.0)	23 (22.1)	52 (20.2)	19 (14.1)	0.04	18 (13.3)	2 (7.1)	7 (7.8)	5 (3.0)	<0.01
Chronic lung disease	27 (15.7)	17 (16.3)	27 (10.5)	9 (6.7)	0.62	33 (24.4)	1 (3.6)	8 (8.9)	2 (1.2)	<0.01
Coronary artery disease	47 (27.3)	31 (29.8)	85 (32.9)	44 (32.6)	<0.01	36 (26.7)	8 (28.6)	25 (27.8)	30 (17.8)	0.06
Hemoglobin, g/dL	13.0 (11.9-13.9)	13.0 (12.1-14.1)	13.3 (12.2-14.3)	13.6 (12.7-14.5)	0.41	13.4 (12.1-14.9)	13.7 (12.2-14.6)	13.6 (12.6-14.3)	13.7 (12.8-14.6)	0.62
NT-proBNP, pg/mL[c]	662 (205-1,744)	180 (96.2-665.1)	172.5 (67.8-543.5)	174 (73-380)	0.22	222 (60-790)	91 (46-225)	164 (80.- 397.2)	123 (55-451)	<0.01
eGFR, mL/min/1.73 m^2 [d]	65.1 (48.5-79.2)	69.6 (60.2-85.4)	70.7 (60.3-85.6)	74.1 (62.8-85.9)	<0.01	72.4 (55.2-92.2)	85.5 (63.8-101.7)	69.7 (59.1-81.9)	81.8 (69.7-94.4)	<0.01

Values are median (Q1-Q3) or n (%). [a]*P* value for comparison across HFpEF phenotypes. [b]*P* value for comparison across all groups. [c]Available in 524 patients of HFpEF patients. [d]Estimated with the CKD-EPI 2021 equation.

BMI = body mass index; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PH = pulmonary hypertension; PVD = pulmonary vascular disease.

RV-FAC <35%, tricuspid annular plane systolic excursion ≤17 mm, tricuspid valve tenting height >9 mm, mid-RV diameter >38 mm, or end-systolic RA area-to-RV area ratio <1.5; otherwise, TR was classified as atrial STR (A-STR).[17,18] The presence of RA or tricuspid annular dilation was required in the definition of ≥moderate A-STR, with cutoffs of RA volume ≥29 mL/m^2 in women and ≥34 mL/m^2 in men or tricuspid annulus apical 4-chamber end-diastolic diameter ≥40 mm or ≥22 mm/m^2 in men and ≥35 mm or ≥21 mm/m^2 in women, as previously recommended.[18] Notably, according to expert consensus, the presence of PH alone was not considered to meet the criteria for V-STR in patients with HFpEF.[17,18] In a sensitivity analysis, V-STR was defined as requiring at least 2 of the 5 above criteria.

RHC AND DIAGNOSTIC CLASSIFICATION. RHC was performed in the supine position; technical details are included in Supplemental Appendix 1. Using invasive hemodynamic data obtained during RHC, we defined HFpEF by PAWP of ≥15 mm Hg at rest, ≥19 mm Hg on feet-up maneuver, or ≥25 mm Hg during exercise.[8] HFpEF was classified as "rest HFpEF" when PAWP at rest was ≥15 mm Hg and as "exercise HFpEF" when PAWP at rest was <15 mm Hg but PAWP was ≥19 mm Hg on feet-up maneuver or ≥25 mm Hg with exercise.[22] PH was defined as mean pulmonary arterial pressure (mPAP) >20 mm Hg at rest. In the absence of PH criteria at rest, exercise-induced PH was defined using an mPAP-to-cardiac output slope of >3 mm Hg/L per min. Precapillary PH (or combined post- and precapillary PH in the setting of HFpEF) was defined with pulmonary vascular resistance (PVR) >2 WU. In a sensitivity analysis, the older PVR cutoff value of >3 WU was used to increase specificity.[22] PH in the absence of HFpEF and with normal PVR was referred to as unclassified PH. In the absence of HFpEF or PH at rest or exercise, patients were defined as noncardiac dyspnea patients based on normal cardiac hemodynamic evaluation.

HFpEF was classified into 4 phenotypes according to the presence or absence of: 1) PVD,[16,23-25] reflected by PVR >2 WU; and 2) rest vs exercise-only elevation in PAWP.[14,26,27] These included HFpEF at rest with PVR >2 (rest HFpEF + PVD), HFpEF at feet-up/exercise and PVR >2 WU (exercise HFpEF + PVD), HFpEF at rest with PVR ≤2 WU (rest HFpEF − PVD), and feet-up/exercise HFpEF with PVR ≤2 WU (exercise HFpEF − PVD).

The remaining patients without HFpEF were classified into 4 categories: precapillary PH (mPAP at rest >20 mm Hg and PVR >2 WU), unclassified PH (mPAP

TABLE 2 Echocardiographic and Hemodynamic Parameters Among Patients With and Without HFpEF

	Phenotypes of HFpEF				
	Rest HFpEF + PVD (n = 172)	Exercise HFpEF + PVD (n = 104)	Rest HFpEF − PVD (n = 258)	Exercise HFpEF − PVD (n = 135)	*P* Value[a]
TR severity					<0.01
None	56 (32.6)	52 (50.0)	171 (66.3)	89 (65.9)	
Mild	58 (33.7)	33 (31.7)	57 (22.1)	37 (27.4)	
Moderate	41 (23.8)	15 (14.4)	20 (7.8)	6 (4.4)	
Moderately severe/severe	17 (9.9)	4 (3.8)	10 (3.9)	3 (2.2)	
≥Moderate TR	58 (33.7)	19 (18.3)	30 (11.6)	9 (6.7)	<0.01
≥Mild TR	116 (67.4)	52 (50.0)	87 (33.7)	46 (34.1)	<0.01
LV ejection fraction, %	63 (59-66)	63 (60-65)	62 (60-65)	63 (60-65)	0.80
LVEDD, mm	48 (45-52)	48 (45-51)	50 (48-54)	49 (46-53)	<0.01
LVESD, mm	31 (28-34)	30 (29-33)	32 (30-35)	32 (29-35)	<0.01
Medial e velocity, cm/s	7 (5-8)	7 (6-8)	8 (6-9)	7 (6-9)	<0.01
Medial E/e ratio	13.3 (11.3-18.0)	10.0 (8.6-12.9)	10.0 (8.3-12.9)	8.9 (7.8-12.0)	<0.01
TR velocity, m/s	3.1 (2.8-3.6)	2.7 (2.5-3.0)	2.6 (2.4-2.8)	2.4 (2.2-2.7)	<0.01
RA pressure at rest, mm Hg	12 (9-14)	7 (5-9.5)	11.5 (9-14)	7 (5-9)	<0.01
RA pressure during exercise, mm Hg	22 (18-27)	17 (14-20)	20 (16-24)	15 (12-18.8)	<0.01
PAWP at rest, mm Hg	19 (16-22)	11 (9-13)	18 (16-20)	12 (10-13)	NA
PAWP at exercise, mm Hg	30 (25-34)	27 (25-32)	31 (26-36.8)	28 (26-32)	<0.01
Mean PA pressure at rest, mm Hg	35 (30-42)	23 (21-27)	25.7 (23-29)	19 (17-21)	<0.01
Mean PA pressure at exercise, mm Hg	54 (48-62)	45 (40-50)	45 (39-52)	40.7 (36-46)	<0.01
PVR, WU	3.2 (2.5-4.4)	2.6 (2.3-3.3)	1.1 (0.8-1.5)	1.4 (1.1-1.7)	NA
CO at rest, L/min	4.6 (3.9-5.6)	4.7 (4.0-5.5)	5.8 (4.9-7.0)	5.5 (4.7-6.3)	<0.01
CO at peak exercise, L/min	7.2 (5.5-8.9)	8.8 (6.8-10.6)	10.1 (8.2-12.5)	10.1 (8.2-12.0)	<0.01
RAP to PAWP ratio at rest	0.6 (0.5-0.7)	0.7 (0.6-0.8)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.03
RAP to PAWP ratio pressureduring exercise	0.7 (0.6-0.9)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.5 (0.4-0.6)	<0.01
LV transmural pressureat rest, mm Hg	7.0 (5.0-10.0)	3.0 (2.0-5.0)	7.0 (5.0-9.0)	4.0 (3.0-6.0)	<0.01
LV transmural pressureduring exercise, mm Hg	9.0 (2.0-13.0)	12.0 (7.0-15.8)	11.0 (7.2-15.0)	13.0 (9.5-17.0)	<0.01

Values are n (%) or median (Q1-Q3). [a]*P* value for comparison across HFpEF phenotypes. [b]*P* value for comparison across all groups.

CO = cardiac output; LV = left ventricular; LVEDD = left ventricular end diastolic dimension; LVESD = left ventricular end systolic dimension; PA = pulmonary artery; PAWP = pulmonary arterial capillary pressure; PVR = pulmonary vascular resistance; RA = right atrial; RAP = right atrial pressure; TR = tricuspid regurgitation; other abbreviations as in Table 1.

Continued on the next page

at rest >20 mm Hg and PVR ≤2 WU), exercise-induced PH without HFpEF, and normal hemodynamics.

The RV-FAC-to-mPAP ratio was calculated as a measure to reflect RV-pulmonary artery coupling and compare it between groups. LV transmural pressure was calculated as PAWP minus RA pressure.

FOLLOW-UP. The index examination (time zero) was the time of the invasive hemodynamic assessment. The primary outcome endpoint was a composite of all-cause mortality and HF hospitalizations. Secondary outcome endpoints included all-cause mortality and HF hospitalizations individually. The primary exposure for these endpoints was ≥moderate TR and its different mechanisms (A-STR and V-STR).

STATISTICAL ANALYSIS. The primary prespecified aims of the analyses were to: 1) study the prevalence of ≥moderate TR among the different phenotypes of HFpEF according to PVD and rest vs exercise elevation in PAWP, and among other causes of PH and patients with noncardiac dyspnea; 2) evaluate and characterize the mechanism of ≥moderate TR based on current recommendations to stratify TR into A-STR and V-STR in HFpEF; and 3) assess the prognostic value of the different mechanisms of ≥moderate TR in HFpEF. Secondary prespecified aims were to: 1) study the prevalence of ≥mild TR and moderate-severe/severe TR in the stated groups; and 2) compare the frequency of TR among patients with exercise-only HFpEF/PH and patients with otherwise normal hemodynamics. No adjustment for multiple hypothesis testing was performed, and the results should be considered in light of that.

All statistical analyses were performed using R version 4.3.1 (R Foundation) or JMP version 17.2.0

TABLE 2 Continued

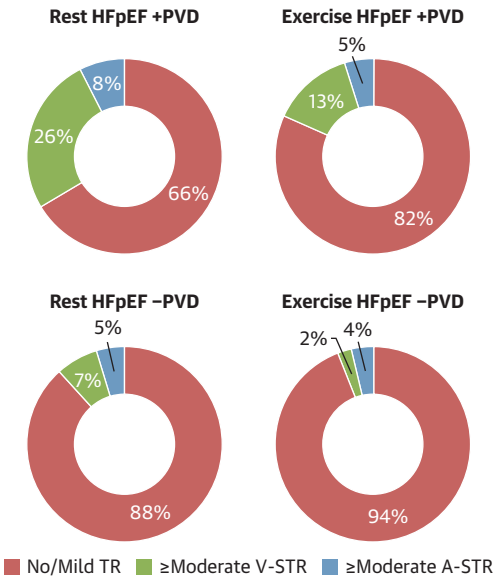
No HFpEF				
Precapillary PH (n = 135)	Unclassified PH (n = 28)	Exercise PH Without HFpEF (n = 90)	Noncardiac Dyspnea (n = 169)	*P* Value[b]
				<0.01
56 (41.5)	19 (67.9)	50 (55.6)	123 (72.8)	
49 (36.3)	7 (25.0)	23 (25.6)	35 (20.7)	
18 (13.3)	2 (7.1)	13 (14.4)	11 (6.5)	
12 (8.9)	0 (0.0)	4 (4.4)	0 (0.0)	
30 (22.2)	2 (7.1)	17 (18.9)	11 (6.5)	<0.01
79 (58.5)	9 (32.1)	40 (44.4)	46 (27.2)	<0.01
64.0 (60.0-66.0)	63.5 (58.5-65.8)	63.0 (60.0-65.0)	62.0 (59.0-65.0)	0.88
46.0 (44.0-50.0)	49.0 (46.0-51.0)	47.0 (44.5-51.0)	48.0 (44.8-51.0)	<0.01
29.0 (27.0-32.0)	31.0 (29.0-34.0)	31.0 (28.0-32.0)	31.0 (28.0-34.0)	<0.01
7.0 (6.0-9.0)	9.0 (7.0-11.0)	7.0 (6.0-8.2)	9.0 (7.0-10.0)	<0.01
8.9 (7.1-12.2)	8.9 (8.0-11.3)	10.0 (7.5-12.3)	7.8 (6.7-10.0)	<0.01
3.1 (2.8-3.5)	2.5 (2.3-2.7)	2.5 (2.3-2.7)	2.3 (2.2-2.5)	<0.01
7 (5-9)	7.5 (6-8)	5 (3-7)	5 (4-7)	<0.01
13 (11-19)	11 (5.8-15.2)	11.5 (9-14)	9 (7-11)	<0.01
9.0 (8.0-12.0)	11.0 (10.0-12.0)	7.5 (6.0-10.0)	9.0 (7.0-10.0)	<0.01
16.0 (13.0-20.0)	18.0 (14.0-20.2)	18.0 (14.0-22.0)	15.0 (11.0-18.0)	<0.01
29.0 (24.0-39.0)	22.0 (21.0-25.0)	16.0 (14.0-18.0)	16.0 (14.0-18.0)	<0.01
48.0 (38.8-59.2)	34.0 (30.7-36.5)	32.5 (28.0-37.0)	25.0 (21.0-30.0)	<0.01
3.8 (2.8-6.6)	1.6 (1.4-1.8)	1.7 (1.4-2.1)	1.4 (1.0-1.8)	<0.01
4.8 (3.9-5.8)	6.8 (6.1-7.7)	4.8 (4.0-5.7)	5.3 (4.6-6.3)	<0.01
8.7 (6.2-10.8)	11.4 (9.9-13.2)	8.4 (7.4-10.1)	11.2 (9.4-12.9)	0.44
0.7 (0.6-0.9)	0.7 (0.6-0.7)	0.7 (0.4-0.9)	0.7 (0.5-0.8)	<0.01
0.8 (0.6-1.1)	0.6 (0.4-0.7)	0.6 (0.5-0.8)	0.6 (0.5-0.8)	<0.01
3.0 (1.0-4.0)	4.0 (3.0-5.0)	2.5 (1.0-4.0)	3.0 (1.2-4.0)	<0.01
3.0 (−1.0-6.0)	7.0 (6.0-9.8)	7.0 (4.0-10.0)	6.0 (3.0-9.0)	<0.01

(JMP Statistical Discovery). Two-sided $P < 0.05$ was considered to be statistically significant. Analysis of variance or Kruskal-Wallis tests were used to compare continuous variables across groups, and the chi-square test was used to compare categoric variables. Kaplan-Meier curves were used for unadjusted survival analyses for death and the composite endpoint with the use of log-rank tests. Cumulative incidence rate curves accounting for competing risks of death were built for outcome of HF hospitalizations with *P* values calculated with the use of the Fine-Gray test. Cox regression models were used for survival analyses including other covariates; both cause-specific and Fine Gray subdistribution HRs were reported for HF hospitalizations. In Cox regression, analysis was adjusted to clinically important variables determined on an a priori basis while avoiding collinearity. These covariates included age, sex, body mass index (BMI), estimated glomerular filtration rate, AF, chronic lung disease, RV-FAC, PVR, mPAP, and NT-proBNP (model 1 covariates). Given collinearity, PAWP and RA pressure were not included in the model. In a sensitivity analysis, HFpEF phenotype was used in place of PVR and mPAP (model 2). Variables with >10% missing data (eg, NT-proBNP) were imputed using the median value. Otherwise, complete case analysis was used. The proportional hazards assumption was tested using the cox.zph function from the "survival" package in R and was met in all Cox models.

RESULTS

BASELINE CHARACTERISTICS. A total of 1,091 patients met the eligibility criteria and were included (Tables 1 and 2). Overall median age was 65 years (Q1-Q3: 54-72 years), and 658 (60.3%) were women. Only 63 patients had an echocardiogram from an

FIGURE 1 Prevalence and Types of ≥Moderate TR (A-STR and V-STR) Across HFpEF Phenotypes



A-STR = atrial secondary tricuspid regurgitation; HFpEF = heart failure with preserved ejection fraction; PVD = pulmonary vascular disease; TR = tricuspid regurgitation; V-STR = ventricular secondary tricuspid regurgitation.

inpatient setting, among whom only 5 had ≥moderate TR; the rest of the patients had outpatient echocardiograms. Of the 1,091 patients, 669 (61.3%) were found to have HFpEF: rest HFpEF + PVD in 172 (25.7%), exercise HFpEF + PVD in 104 (15.5%), rest HFpEF − PVD in 258 (38.6%), and exercise HFpEF − PVD in 135 (20.2%) (**Tables 1 and 2**). Notably, all patients with rest HFpEF + PVD had mPAP >20 mm Hg, meeting the criteria for combined pre- and postcapillary PH. Among the 422 patients who did not have HFpEF, 135 (32.0%) had rest precapillary PH, 28 (6.6%) had unclassified PH, 90 (21.3%) had exercise PH without HFpEF, and 169 (40.0%) had normal hemodynamics at rest and exercise (**Tables 1 and 2**).

Among patients with HFpEF, those with HFpEF and PVD were generally older, more likely women, had lower BMI, and had more frequent AF and chronic lung disease compared with patients with HFpEF and no PVD (**Table 1**, Supplemental Table 1, Supplemental Figure 1). Patients with exercise-only HFpEF generally had less AF, chronic kidney disease, and diabetes mellitus and lower BMI compared with patients with rest HFpEF (**Table 1**, Supplemental Table 1). Among the 4 phenotypes of HFpEF, those with exercise HFpEF − PVD had the lowest prevalence of AF and comorbidities (**Table 1**). As expected, resting RA pressure was higher with rest vs exercise phenotypes of HFpEF, but in all 4 phenotypes it doubled with exercise (**Table 2**). LV transmural pressure increased with exercise in all HFpEF phenotypes (**Table 2**).

Compared with patients with HFpEF, patients without HFpEF generally had lower BMI and lower prevalence of hypertension and AF. Patients with unclassified PH or normal hemodynamics were relatively young with low comorbidity burden (**Tables 1 and 2**).

PREVALENCE OF TR AMONG PATIENTS WITH AND WITHOUT HFpEF. Among the 669 patients with HFpEF, 301 (45.0%) had ≥mild TR, 116 (17.4%) had ≥moderate TR, and 34 (5.1%) had moderately severe or severe TR (**Table 2**). Moderate or greater TR (**Figure 1**) was most prevalent in patients with rest HFpEF + PVD, occurring in 33.7% of those patients, followed by exercise HFpEF + PVD (18.3%) (**Table 2**). Patients without PVD had a lower prevalence of moderate or greater TR, which occurred in 11.6% of patients with rest HFpEF − PVD and 6.7% of patients with exercise HFpEF − PVD. Notably, the association of PVD with at least moderate TR was stronger than the association of rest (vs exercise) HFpEF (Supplemental Table 2). Similar trends were observed for mild or greater TR as well as for moderately severe/severe TR) (**Table 2**).

Among the patients without HFpEF, patients with isolated precapillary PH had the second highest prevalence of moderate or severe TR after rest HFpEF + PVD, observed in 22.2%. Moderate or greater TR was present in 7.1% of patients with unclassified PH and 6.5% of patients with normal hemodynamics (**Table 2**). Similar trends were observed for mild or greater TR and moderately severe/severe TR (**Table 2**). Notably, exercise-only HFpEF had greater severity of STR ($P = 0.005$) compared with noncardiac dyspnea patients, with a higher prevalence of ≥moderate TR (11.7% vs 6.5%; $P = 0.047$) and of ≥mild TR (41.0% vs 27.2%; $P = 0.001$). A sensitivity analysis using a PVR cutoff of 3 WU instead of 2 WU showed similar results (Supplemental Tables 3 and 4).

Notably, there was near perfect agreement between the reported and the de novo assessed TR severity grade (no, mild, moderate, moderate-severe/

severe) in the 100-patient sample with Cohen's kappa of 0.96 (95% CI: 0.92-1.00).

CHARACTERISTICS AND MECHANISMS OF TR IN HFpEF. Among patients with HFpEF, those with ≥moderate TR were generally older, more frequently women with smaller LV dimensions, lower BMI, more AF, larger RA volume, higher E/e′ ratio and TR velocity on echocardiography, and higher resting PAWP, resting mPAP, exercise mPAP, and PVR compared with patients with HFpEF and no or mild TR (**Table 3**). There were no differences in exercise PAWP or in rest or exercise cardiac index in patients with or without TR (**Table 3**), likely because most TR cases were moderate rather than severe (**Table 2**). There was good interobserver reliability for offline measurements (ICCs: 0.74 for RV end-diastolic area, 0.82 for RV end-systolic area, 0.84 for RA volume, 0.81 for RA-to-RV end-systolic area ratio, and 0.86 for tenting height of tricuspid leaflets). In addition, reproducibility of reported tricuspid annular plane systolic excursion was evaluated in a 10-patient sample and the ICC was 0.96.

Of the 116 patients with HFpEF and ≥moderate TR, A-STR was present in 35 (30.2%) and V-STR in 80 (69.0%); 1 patient did not have enough obtainable data to classify type of TR. Compared with V-STR, patients with A-STR were more likely to be women, had lower rest and exercise mPAP, lower PVR, lower RA pressure (which was similar to patients with no/mild TR), and, by definition, better RV function and smaller RV size (**Table 3**, Supplemental Figure 2). Interestingly, patients with ≥moderate A-STR and V-STR had similar age and prevalence of AF (54.3% and 48.8%, respectively), and patients with V-STR had larger RA volume (median 88.6 mL vs 65.0 mL; $P = 0.04$) (Supplemental Figure 2).

Notably, when considering the different phenotypes of HFpEF, the prevalence of ≥moderate V-STR in patients with HFpEF and PVD (rest or exercise) was approximately 3 times that of A-STR (Supplemental Tables 1 and 5, **Figure 1**, Supplemental Figure 3). Importantly, the difference in prevalence of TR between phenotypes of HFpEF was mainly related to difference in prevalence of V-STR, rather than A-STR, across the phenotypes (Supplemental Table 5, **Figure 1**), in tandem with differences in RV function.

ASSOCIATION OF TR TYPES WITH OUTCOMES. Over a median 4.9 years (Q1-Q3: 3.1-7.1 years) of follow-up, there were 100 deaths and 96 HF hospitalizations. The composite endpoint occurred in 154 patients. The presence of ≥moderate TR was associated with increased risk of the composite endpoint (HR: 2.55; 95% CI: 1.80-3.59; $P < 0.01$). The presence of ≥moderate V-STR and A-STR was associated with increased risk of the composite endpoint vs no/mild TR (V-STR: HR: 2.84 [95% CI: 1.94-4.15; $P < 0.01$]; A-STR: HR: 1.96 [5% CI: 1.05-3.64; $P = 0.03$]) (**Figure 2**). In multivariable Cox analysis, ≥moderate V-STR remained associated with the composite endpoint, whereas the association of ≥moderate A-STR was weakened (model 1: V-STR HR: 1.70 [95% CI: 1.10-2.65]; A-STR HR: 1.67 [95% CI: 0.85-3.29]) (**Table 4**). In multivariable analysis including covariates of model 1 except for the continuous RV-FAC variable, there was no interaction between abnormal RV-FAC (cutoff <35%) and V-STR (vs no/mild STR) in relation to the composite endpoint ($P = 0.60$). Testing the interaction between RV-FAC <35% and A-STR was not feasible, because all of those patients had RV-FAC ≥35%.

Moderate or greater V-STR was associated with mortality individually compared with no/mild TR (HR: 3.41; 95% CI: 2.19-5.35; $P < 0.001$), whereas ≥moderate A-STR was not significantly associated with mortality ($P = 0.37$) (**Figure 2**). On multivariable analysis, ≥moderate V-STR remained associated with mortality compared with no/mild TR (Supplemental Table 6). Both ≥moderate V-STR and A-STR were associated with increased HF hospitalizations compared with no/mild TR at the univariate level (Fine-Gray subdistribution HRs: V-STR: 2.82 [95% CI: 1.74-4.55; $P < 0.01$]; A-STR: 2.89 [95% CI: 1.51-5.51; $P < 0.01$]) (**Figure 2**) and the multivariable level (Supplemental Table 7).

ADDITIONAL SENSITIVITY ANALYSES. Sensitivity analyses where V-STR was categorized more stringently, HFpEF was defined exclusively by exercise (without leg elevation), or echocardiograms were confined to <30 days before invasive assessment showed that findings did not meaningfully differ from the primary analysis (Supplemental Appendix 2, Supplemental Tables 8 to 13).

DISCUSSION

In this study, we evaluated the prevalence, mechanisms, and prognostic significance of STR across the spectrum of HFpEF, as stratified by invasively assessed presence or absence of PVD and rest vs exercise-only elevation in left-side filling pressure (**Central Illustration**). Our major findings were: 1) there was significant variability in prevalence of ≥moderate STR across HFpEF phenotypes, ranging from 6.7% in those with exercise HFpEF − PVD to 33.7% in patients with rest HFpEF + PVD, mainly related to differing prevalence of V-STR rather than A-STR, which was mainly driven by PVD to a greater

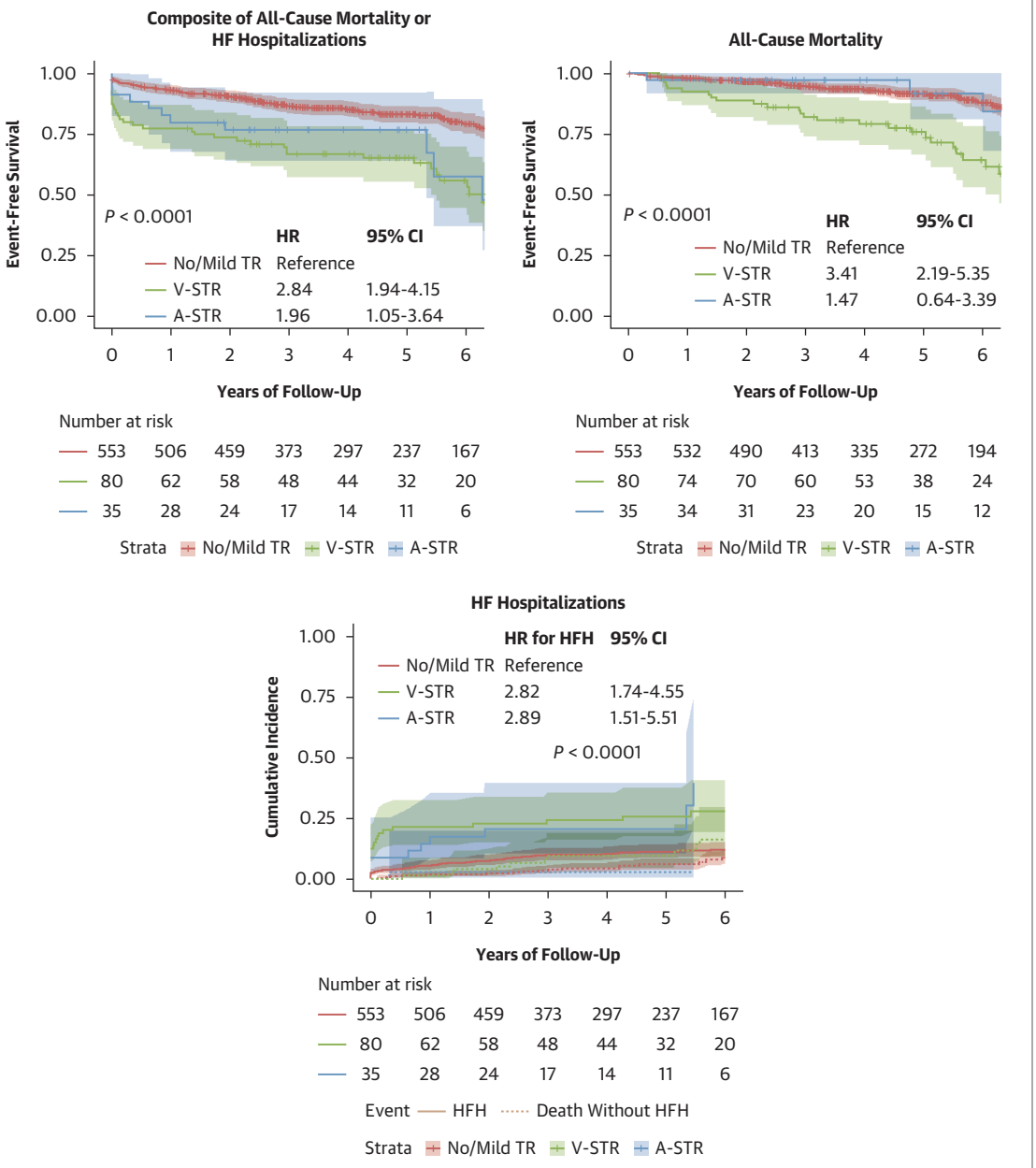
TABLE 3 Characteristics of Patients With HFpEF by Presence and Type of TR

	No TR (n = 371)	Mild TR (n = 182)	A-STR (n = 35)	V-STR (n = 80)	*P* Value
Age, y	65 (56-70)	69.5 (62-75)	72 (65.5-78)	71 (66-77.2)	<0.01
Female	187 (50.4)	119 (65.4)	31 (88.6)[a]	52 (65.0)	<0.01
BMI, kg/m^2	34.0 (29.2-39.4)	32.2 (27.1-37.8)	29.3 (25.0-34.2)	30.9 (25.5-36.7)	<0.01
Diabetes mellitus	83 (22.4)	47 (25.8)	7 (20.0)	21 (26.2)	0.71
Hypertension	173 (46.6)	87 (47.8)	19 (54.3)	36 (45.0)	0.82
Sleep apnea	121 (32.6)	59 (32.4)	7 (20.0)	20 (25.0)	0.27
Ischemic stroke	14 (3.8)	7 (3.8)	2 (5.7)	4 (5.0)	0.91
Atrial fibrillation	56 (15.1)	46 (25.3)	19 (54.3)	39 (48.8)	<0.01
Chronic lung disease	40 (10.8)	23 (12.6)	7 (20.0)	10 (12.5)	0.43
Coronary artery disease	115 (31.0)	60 (33.0)	9 (25.7)	22 (27.5)	0.74
Hemoglobin, g/dL	13.4 (12.4-14.5)	13.0 (11.9-13.9)	13.0 (12.1-13.7)	12.8 (11.6-13.8)	<0.01
NT-proBNP, pg/mL	145 (67.2-443.8)	292 (139.5-614.8)	405.5 (213.5-905.8)[a]	1030 (390-2329)	<0.01
eGFR, mL/min/1.73 m^2	71.1 (60.2-87.3)	68.1 (57.4-84.0)	67.3 (57.0-79.2)	65.6 (49.5-79.0)	<0.01
LV ejection fraction, %	62 (59-65)	63 (60-66)	63 (60-65)	63 (60-66)	0.24
LVEDD, mm	50 (47-54)	48 (46-52)	47 (44-49)	48 (44-51)	<0.01
LVESD, mm	32 (29-35)	31 (29-34)	29.5 (27.2-32)	31 (28-34)	<0.01
Medial e velocity, cm/s	7 (6-9)	7 (6-8)	8 (7-9.5)[a]	7 (5-8)	<0.01
Medial E/e ratio	10.0 (8.1-12.9)	11.4 (8.9-15.0)	11.3 (8.9-13.4)[a]	13.2 (11.3-16.8)	<0.01
TR velocity, m/sec	2.5 (2.3-2.8)	2.8 (2.6-3.1)	3.1 (2.8-3.3)	3.1 (2.8-3.7)	<0.01
RA end-systolic volume, mL	45.8 (32.7-64.9)	49.0 (36.8-69.0)	65.0 (50.1-105.4)[a]	88.6 (57.8-123.1)	<0.01
RV end-diastolic area, cm^2	24.1 (19.0-28.1)	23.4 (19.6-28.0)	20.6 (18.2-24.4)[a]	27.4 (22.3-34.1)	<0.01
RV end-systolic area, cm^2	13.7 (10.2-17.1)	14.1 (11.5-17.9)	10.5 (9.1-12.9)[a]	17.8 (13.5-23.2)	<0.01
RV-FAC, %	42.1 (35.1-48.6)	39.1 (32.0-45.5)	48.8 (43.4-53.9)[a]	35.7 (26.9-42.9)	<0.01
TV tenting height, mm	2.7 (1.0-7.7)	4.0 (1.0-8.2)	2.3 (1.1-4.0)[a]	4.6 (2.9-7.9)	<0.01
Mid-RV diameter, cm	3.3 (2.8-3.7)	3.4 (3.0-3.7)	3.2 (3.0-3.6)[a]	4.0 (3.3-4.4)	<0.01
RA to RV end-systolic area	1.2 (1.0-1.5)	1.3 (1.0-1.5)	2.0 (1.7-2.3)[a]	1.3 (1.0-1.8)	<0.01
TAPSE, mm	23 (20-25)	23 (20-26)	23 (21-25.2)[a]	19 (15.8-23)	<0.01
PAWP at rest, mm Hg	16 (12-19)	16 (13-20)	18 (14-20.5)	18 (15-21.2)	<0.01
PAWP at exercise, mm Hg	30 (26-35)	29 (25-34)	29 (26-32)	29 (25-34)	0.60
mPAP at rest, mm Hg	24 (21-28.8)	26 (22-34)	28 (24.7-32.5)[a]	33.5 (26.8-43.7)	<0.01
mPAP during exercise, mm Hg	45 (38.3-51)	47 (41-54.1)	42.7 (38.1-48)[a]	53.2 (44.8-62.6)	<0.01
RAP at rest, mm Hg	10 (7-12)	10 (7-12)	10 (8-13)[a]	12.5 (9-17.2)	<0.01
RAP at exercise, mm Hg	18 (15-22)	19 (15-22)	17 (14.5-22)[a]	26 (18-29)	<0.01
PVR, WU	1.5 (1.0-2.1)	1.9 (1.2-2.9)	2.4 (1.4-3.3)[a]	3.3 (2.0-4.6)	<0.01
CO at rest, L/min	5.5 (4.6-6.6)	5.0 (4.2-6.4)	4.6 (3.6-5.5)	4.9 (4.1-5.9)	<0.01
CO during exercise, L/min	10.0 (8.2-12.0)	8.6 (7.2-11.2)	7.1 (5.7-9.0)	6.9 (5.1-8.9)	<0.01
CI at rest, L/min/m^2	2.6 (2.2-3.0)	2.5 (2.2-3.1)	2.4 (2.0-2.8)	2.5 (2.0-2.9)	0.10
CI during exercise, L/min/m^2	4.7 (3.9-5.6)	4.4 (3.7-5.5)	3.9 (2.9-4.8)	3.6 (2.7-4.6)	<0.01
RV-FAC to mPAP ratio	1.7 (1.3-2.0)	1.4 (1.0-2.0)	1.7 (1.4-2.0)[a]	1.0 (0.6-1.4)[a]	<0.01
RAP to PAWP ratio at rest	0.6 (0.5-0.7)	0.6 (0.5-0.8)	0.6 (0.5-0.7)	0.7 (0.6-0.9)[a]	<0.01
RAP to PAWP ratio during exercise	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.8)	0.8 (0.7-1.0)[a]	<0.01
LV transmural pressure at rest, mm Hg	6.0 (4.0-8.0)	6.0 (3.0-9.0)	7.0 (5.0-8.8)	5.0 (2.0-8.0)[a]	0.03
LV transmural pressure during exercise, mm Hg	12.0 (8.0-16.0)	11.0 (8.0-15.0)	11.0 (6.5-16.5)	7.0 (2.0-11.0)[a]	<0.01
Phenotypes of HFpEF					<0.01
Rest HFpEF + PVD	14 (3.8)	12 (6.6)	1 (2.9)	8 (10.0)	
Rest HFpEF − PVD	129 (34.8)	56 (30.8)	9 (25.7)	9 (11.2)	
Exercise HFpEF + PVD	19 (5.1)	31 (17.0)	10 (28.6)	34 (42.5)	
Exercise HFpEF − PVD	209 (56.3)	83 (45.6)	15 (42.9)	29 (36.2)	

Values are median (Q1-Q3) or n (%). [a]Different between A-STR and V-STR.

A-STR = atrial secondary tricuspid regurgitation; CI = cardiac index; mPAP = mean pulmonary artery pressure; RV = right ventricular; RV-FAC = fractional area change; TAPSE = tricuspid annular plane systolic excursion; V-STR = ventricular secondary tricuspid regurgitation; TV = tricuspid valve; other abbreviations as in Tables 1 and 2.

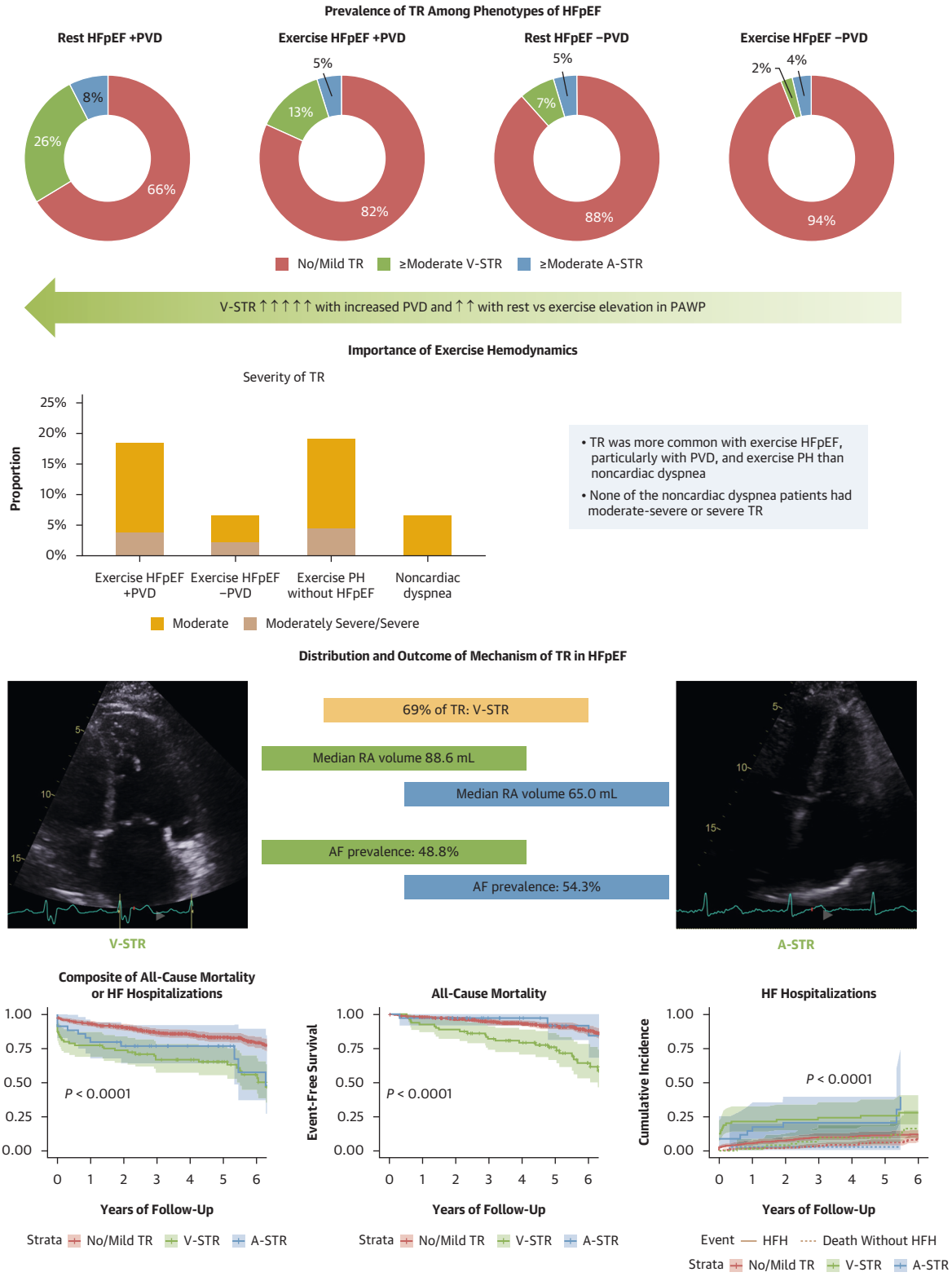
FIGURE 2 Association of TR Type With All-Cause Mortality and Heart Failure Hospitalizations



(Left) Association of V-STR and A-STR with the composite endpoint of all-cause mortality or heart failure (HF) hospitalizations; HRs were calculated using cause-specific HRs. (Bottom) Association of V-STR and A-STR with all-cause mortality; HRs were calculated using cause-specific HRs. (Right) Association of V-STR and A-STR with HF hospitalizations, analyzed using competing risk curves and Fine-Gray model with subdistribution HRs shown. Abbreviations as in Figure 1.

extent than by PAWP; 2) the presence of PVD was also associated with TR in patients without HFpEF; 3) V-STR was the predominant TR type in HFpEF, although atrial myopathy was even greater in those with V-STR than with A-STR, reflected by greater RA dilation, suggesting a mixed mechanism; 4) importantly, ~1 in every 8 patients with exercise-only HFpEF had ≥moderate TR, which was more frequent when in the presence of PVD, compared with patients with normal hemodynamics, highlighting the

CENTRAL ILLUSTRATION Tricuspid Regurgitation Across the Spectrum of Heart Failure With Preserved Ejection Fraction



Naser JA, et al. JACC. 2025;86(24):2495-2508.

AF = atrial fibrillation; A-STR = atrial secondary tricuspid regurgitation; HFH = heart failure hospitalization; HFpEF = heart failure with preserved ejection fraction; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVD = pulmonary vascular disease; RA = right atrial; STR = secondary tricuspid regurgitation; TR = tricuspid regurgitation; V-STR = ventricular secondary tricuspid regurgitation.

importance of evaluation for exercise abnormalities in patients with significant TR; and 5) the presence of ≥moderate V-STR was associated with increased risk of the composite endpoint of mortality and HF hospitalizations, whereas ≥moderate A-STR was associated with increased risk of HF hospitalizations only, indicating differential prognostic impact by TR mechanism. These data underscore the importance of TR in HFpEF and its relationship with PVD, highlight the importance of exercise hemodynamics in TR, and suggest that therapies that can arrest or reverse HFpEF progression and mitigate RV loading across stages may reduce the burden of TR and improve clinical status and outcomes.

PATHOPHYSIOLOGY OF TR IN HFpEF. STR in HFpEF can develop via different mechanisms.[9,13] One is a consequence of advanced HFpEF with pulmonary vascular remodeling leading to RV enlargement and dysfunction, tricuspid leaflet tethering, and tricuspid annulus dilation, resulting in a V-STR phenotype.[5,7,16,28] However, even patients without overt RV dysfunction or enlargement can develop significant TR in the setting of RA enlargement and tricuspid annulus dilation, resulting in an A-STR phenotype.[2,12,13] The associated atrial myopathy is thought to result from the same pathophysiologic process that underlies the development of diastolic dysfunction, including systemic inflammation, excess adipose tissue, and metabolic comorbidities,[29-32] as well as coexistent AF, another consequence and biomarker of atrial myopathy.[2,5,30,33-35]

PREVALENCE OF TR IN HFpEF: IMPORTANCE OF PULMONARY VASCULAR DISEASE. The prevalence of ≥moderate STR in HFpEF has ranged from 18% to 27% in previous reports,[5,28,36,37] which is consistent with the present study. In its earlier stages, HFpEF is characterized by normal natriuretic peptide levels and resting PAWP, with elevation in PAWP during exercise.[14,27,38] The presence of PVD in HFpEF suggests a more advanced disease stage, wherein patients have higher natriuretic peptide levels, worse pulmonary pressures, more RV dysfunction, and worse ventricular interdependence.[16,23] The present study highlights the importance of HFpEF phenotype in association with the prevalence of STR. In patients with elevated PAWP exclusively with exercise[14,26,27] in the absence of PVD,[16,23,24] ≥moderate TR was present in only 6.7% of cases, compared with 33.7% in patients with both rest elevation in PAWP and PVD. Notably, the impact of PVD on the frequency of STR in HFpEF appeared to be stronger than the impact of rest vs exercise-only elevation in PAWP, with 11.6% prevalence of ≥moderate STR in patients with rest HFpEF without PVD (1.7 times that in exercise HFpEF without PVD) compared with 18.3% in patients with exercise HFpEF and PVD (2.7 times that in exercise HFpEF without PVD). This finding could be related to the worse RV remodeling and pressure overload in the setting of increased PVR, leading to worse RV-pulmonary artery coupling and more V-STR in these patients.

IMPORTANCE OF EXERCISE HEMODYNAMICS IN TR. Another notable observation in the present study was that even patients with exercise-only HFpEF may present with significant STR. The prevalences of ≥mild and ≥moderate STR were 41.0%, and 11.7% in patients with exercise-only HFpEF and 44.4% and 18.9% in patients with exercise-only precapillary PH

TABLE 4 Multivariable Cox Model for the Composite of All-Cause Mortality or HF Hospitalization

	HR	Lower CL	Upper CL	*P* Value
Model 1 (no. of events = 145)				
Age[a]	1.00	0.98	1.02	0.96
Female	0.87	0.61	1.24	0.44
eGFR[a]	1.00	0.98	1.03	0.74
BMI[a]	0.99	0.98	1.00	0.02
Atrial fibrillation	1.48	1.01	2.17	0.04
Chronic lung disease	2.01	1.34	3.01	<0.01
RV-FAC[a]	0.99	0.98	1.01	0.52
Type of TR (vs no/mild TR)				
≥Moderate V-STR	1.70	1.10	2.65	0.02
≥Moderate A-STR	1.67	0.85	3.29	0.14
NT-proBNP[a]	1.00	1.00	1.00	0.96
PVR[a]	1.03	0.94	1.13	0.58
Resting mPAP[a]	1.03	1.02	1.05	<0.01
Model 2 (no. of events = 145)				
Age[a]	0.99	0.98	1.01	0.41
Female	0.88	0.61	1.26	0.48
eGFR[a]	1.01	0.99	1.03	0.47
BMI[a]	0.99	0.98	1.00	0.02
Atrial fibrillation	1.50	1.03	2.18	0.04
Chronic lung disease	2.08	1.39	3.10	<0.01
RV FAC[a]	0.99	0.98	1.01	0.48
Type of TR (vs no/mild TR)				
≥Moderate V-STR	2.05	1.34	3.13	<0.01
≥Moderate A-STR	1.74	0.89	3.42	0.10
NT-proBNP[a]	1.00	1.00	1.00	0.72
HFpEF phenotype (reference is exercise HFpEF − PVD)				
Exercise HFpEF + PVD	1.23	0.59	2.57	0.58
Rest HFpEF −PVD	1.47	0.80	2.68	0.21
Rest HFpEF + PVD	2.40	1.29	4.46	0.01

Each variable other than RV-FAC had 154 events; RV-FAC had 145 events due to missing values. [a]HR is presented per unit change.

Abbreviations as in Tables 1-3.

in the absence of HFpEF, compared with 27.2% and 6.5% in patients with noncardiac dyspnea. Although the prevalence of STR was similar between patients with exercise HFpEF without PVD and those with noncardiac dyspnea, none of the latter group had moderately severe or severe TR, emphasizing the importance of exercise hemodynamics in the evaluation of patients with STR.[14,15,26,27,39] Importantly, LV transmural pressure increased with exercise in patients with exercise HFpEF, arguing against a primary role of pericardial restraint and ventricular interdependence in elevation of PAWP in these patients, although they may contribute in some.

These findings suggest that intervention with medical therapy directed at HFpEF during the early stages or phenotypes of HFpEF (eg, exercise-only HFpEF, no PVD) could mitigate or even prevent progression of STR, underscoring the importance of early recognition and diagnosis of HFpEF to implement treatment.

DISTRIBUTION OF MECHANISMS OF TR IN HFpEF. As currently defined, STR was found to be predominantly related to the ventricular secondary mechanism in patients with HFpEF (69% of ≥moderate STR), and the prevalence of V-STR varied significantly with the phenotype of HFpEF, related to varying prevalence of PVD and RV dysfunction. The prevalence of A-STR was less variable between HFpEF phenotypes. Notably, despite this predominance of V-STR, there was clear evidence of atrial myopathy in patients with V-STR, including greater RA dilation and similar prevalence of AF. These findings suggest the presence of mixed mechanisms of STR in patients with HFpEF meeting the current criteria for V-STR and that it may be too simplistic to classify patients with STR in HFpEF into either V-STR or A-STR. Because of the cross-sectional nature of the study, the contribution from RV dysfunction and PH to the RA myopathy and STR compared with an initial A-STR phenotype complicated by RV volume overload from STR and subsequent RV dysfunction in later stages cannot be determined, although the association of V-STR prevalence with PVD among HFpEF phenotypes suggests an important potential contribution of pulmonary pressures to the TR.

Importantly, history of AF was absent in 46% of patients with ≥moderate A-STR, which is notable given that current guidelines use AF history to define A-STR.[40] There was also a similar frequency of AF in patients with A-STR and V-STR, highlighting the lack of sensitivity and specificity of AF in diagnosing the mechanism of STR.

IMPLICATIONS OF TR MECHANISM ON CLINICAL OUTCOMES. STR has been recognized as a marker of more advanced HFpEF,[28,37,41,42] but there is limited and conflicting evidence whether the association between STR and outcomes is independent from RV dysfunction and whether there is a differential impact of A-STR vs V-STR.[2,43] In the present study, we show that ≥moderate V-STR was associated with the composite endpoint of death and HF hospitalizations as well as mortality alone compared with no/mild STR, independently from AF, chronic lung disease, HFpEF phenotype, pulmonary pressure, PVR, RV function, and NT-proBNP level. A-STR was also clearly associated with worse rates of HF hospitalizations compared with no TR, without significant relationship to mortality alone, indicating that mechanism of STR may help risk-stratify patients with HFpEF.

STUDY LIMITATIONS. This was a retrospective study involving all Mayo Clinic sites, some of which are considered tertiary centers, introducing referral bias. All included patients were referred in routine clinical practice for invasive hemodynamic evaluation that included both rest and exercise assessments, introducing selection bias. However, without such assessment, definitive diagnosis of HFpEF and its various phenotypes (compared with other causes of PH) would be unreliable. The study evaluated prevalent rather than incident TR, and survival bias affecting prevalence of TR and distribution of its types cannot be excluded. However, studying incident TR in HFpEF would require a much larger sample size and serial or longitudinal exercise invasive hemodynamic assessments, which are not currently available. Given the retrospective nature of the study, obtaining 3-dimensional echocardiographic data sets to evaluate RA and RV volumes was not possible. There was a small number of patients with HFpEF and ≥moderate A-STR, which likely reduced statistical power in some analyses. Transthoracic echocardiograms were interpreted by multiple echocardiologists, and interobserver variability is possible. However, echocardiographic grading of TR remained consistent among Mayo Clinic sites in the study period, and reproducibility of TR severity assessment in a 100-patient sample was near perfect. Furthermore, RA and RV measurements were performed by 4 readers for this study, with good interobserver reliability. We used International Classification of Diseases codes to identify many comorbidities, with the potential of underestimating their prevalence.

CONCLUSIONS

Clinically significant STR was present in 17% of patients with invasively diagnosed HFpEF, with wide variability across the phenotypes of HFpEF, ranging from 6.7% to 33.7%, mainly related to differing prevalence of V-STR than of A-STR. STR was mainly driven by PVD, to a greater extent than by PAWP. Patients with exercise-only HFpEF and exercise-only PH had more STR compared with noncardiac dyspnea patients, and no noncardiac dyspnea patients had moderate-severe or severe TR. This indicates that it is unusual for significant STR to exist in isolation, and its presence should prompt further evaluation, including assessment of exercise hemodynamics. Most patients with HFpEF and STR have V-STR, although these patients display more atrial remodeling than with A-STR, suggesting a mixed mechanism. Finally, the presence of V-STR conferred greater risk of mortality and HF hospitalizations, whereas A-STR conferred greater risk of HF hospitalizations only, suggesting that mechanism classification may help in risk-stratifying patients.

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