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ORIGINAL RESEARCH

Nonischemic Septal Fibrosis in Functional Tricuspid Regurgitation Provides Incremental Stratification of Adverse Remodeling and Prognosis

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ABSTRACT

BACKGROUND Functional tricuspid regurgitation (TR) arises from impaired valve integrity resulting from contractile dysfunction, chamber dilation, or myocardial tissue alterations. Whereas right ventricular (RV) dysfunction is a recognized driver of adverse outcomes in TR, the impact of myocardial tissue injury, particularly nonischemic septal fibrosis (NIsF), remains largely unexplored.

OBJECTIVES This study aims to evaluate the association of NIsF with adverse right-sided chamber remodeling and to assess its incremental prognostic value for mortality in patients with functional TR.

METHODS Patients with advanced (≥ moderate) functional TR underwent comprehensive cardiac magnetic resonance (CMR) evaluation. Late gadolinium enhancement (LGE) was used to identify NIsF, defined as hyperenhancement in the midmyocardial or epicardial regions of the interventricular septum. Cine CMR measured functional and geometric indices of the left and right sides of the heart. Follow-up data were obtained for all-cause mortality.

RESULTS A total of 663 patients with advanced TR (mean age: 63.8 ± 16.0 years; 53% male) were studied, and 29.4% were found to have NIsF. NIsF was strongly associated with adverse chamber remodeling, including larger left ventricular and RV volumes, reduced systolic function, and increased TR severity (all $P < 0.001$). TR regurgitant fraction increased stepwise with NIsF extent (no NIsF, 34.9% ± 1.5%; 1 segment, 38.1% ± 13.0%; 2 segments, 40.8% ± 13.8%; $P < 0.001$). Over a mean follow-up of 4.3 ± 4.3 years, 25.3% of patients died. NIsF was independently associated with mortality (HR: 1.79 [95% CI: 1.26-2.56]; $P = 0.001$), even after adjusting for conventional risk markers, including age, TR severity, RV dysfunction, and dilation. Kaplan-Meier analysis demonstrated significantly higher mortality risk among patients with NIsF compared with patients without NIsF ($P < 0.001$).

CONCLUSIONS Among patients with advanced TR, NIsF is an important marker of adverse right-sided chamber remodeling and provides incremental prognostic utility beyond conventional risk markers. (JACC Cardiovasc Imaging. 2025;■:■-■) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

LGE = late gadolinium enhancement

LV = left ventricular

NIsF = nonischemic septal fibrosis

RV = right ventricular

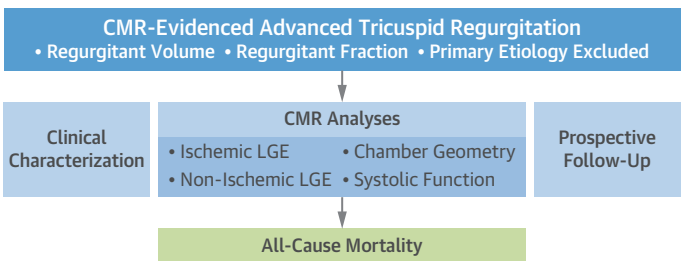
TR = tricuspid regurgitation

Tricuspid regurgitation (TR) is a leading cause of valvular heart disease. In the United States alone, nearly 2 million people have advanced (> mild) TR without intrinsic tricuspid valve disease ("functional TR") among whom advanced TR is linked to progressive heart failure and a threefold increase in mortality risk.[1] Despite the clinical impact of TR, the mechanisms driving disease progression and factors predicting outcomes in TR remain poorly understood. Current prognostic models that incorporate traditional markers such as right ventricular (RV) size and function have yielded inconsistent results,[2,3] thus highlighting the need for more specific and mechanistically relevant markers of disease severity.

In left-sided valvular heart disease, myocardial injury in the subvalvular myocardium has been identified as a key driver of adverse remodeling and poor outcomes, as demonstrated in studies by our group and others.[4-6] In the context of TR, the interventricular septum plays a unique role as a shared boundary between the right and left ventricles, thereby making it particularly susceptible to mechanical stress and maladaptive remodeling.[7,8] The role of septal injury in the progression and outcomes of TR has not been studied, despite its potential significance in driving TR severity and contributing to chamber remodeling.

Cardiac magnetic resonance (CMR) offers a powerful tool to assess myocardial tissue properties, chamber geometry, and function, as well as TR itself. Regarding tissue characterization, late gadolinium enhancement (LGE) CMR is well validated to characterize both the presence and the pattern of myocardial injury, including both ischemic and nonischemic fibrosis. Nonischemic septal fibrosis (NIsF), a distinct pattern of midmyocardial or epicardial fibrosis within the septum, has been shown to correlate with histopathologic findings, predict outcomes in heart failure cohorts,[9] and be associated with increased RV wall stress.[10,11] Despite these established associations, the role of NIsF in TR has not been investigated. This study aimed to evaluate the relationship between NIsF and adverse remodeling in patients with advanced functional TR, as well as to assess the incremental prognostic value of NIsF for mortality beyond conventional imaging markers.

FIGURE 1 Study Design



Overall study design entailing image acquisition, analysis, and clinical characterization. CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement.

METHODS

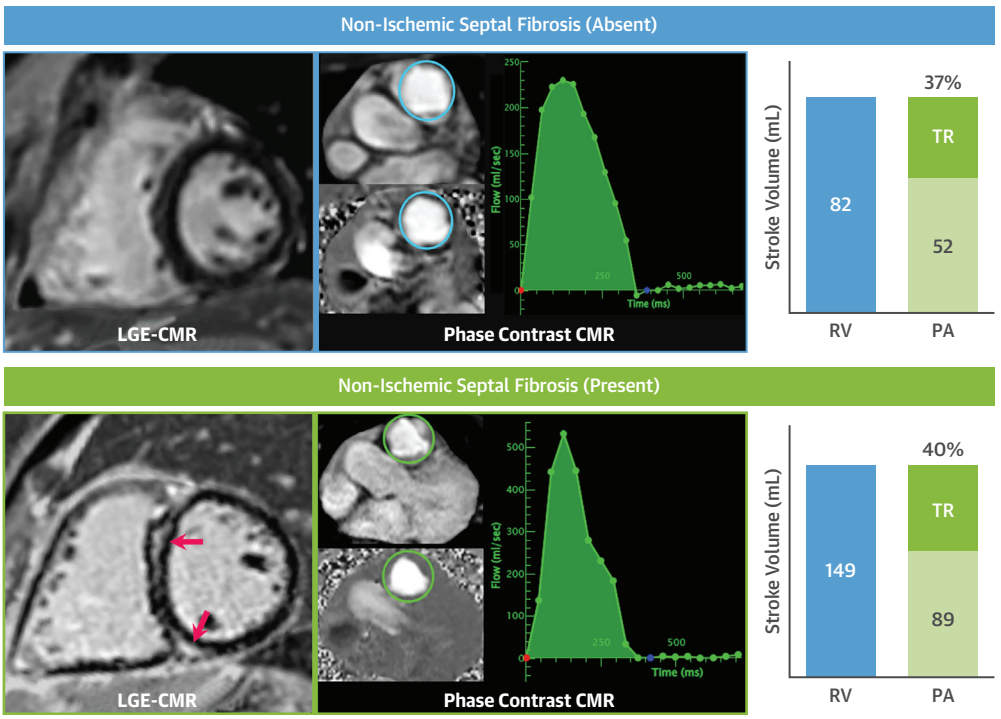
STUDY GROUP. The study group comprised consecutive patients with advanced functional TR (≥ moderate) who underwent CMR at New York Presbyterian Hospital-Weill Cornell Medicine (New York, New York, USA). Patients with previous tricuspid valve surgery, congenital heart disease, or primary tricuspid valvular disease (prolapse, rheumatic, leaflet perforation) were excluded, as were patients with CMR-evidenced conditions that impeded visualization of NIsF and myocardial infarction, including infiltrative cardiomyopathies.

Figure 1 illustrates the study protocol, which includes data acquisition, follow-up, and quantitative CMR analyses. TR severity was assessed by experienced (ACC [American College of Cardiology]/AHA [American Heart Association] level 3) CMR readers using an approach concordant with guidelines for which advanced TR was assessed (see the later section on CMR analysis). For patients with multiple examinations, the initial CMR study demonstrating advanced TR was used for study purposes. Clinical indices were attained through standardized questionnaires (at the time of CMR), supplemented by institutional database queries. Mortality was ascertained through the Social Security Death Index and electronic medical records.

The Weill Cornell Medicine Institutional Review Board provided approval for this study, including a waiver of informed consent for use of preexisting imaging and clinical data as analyzed for research purposes.

CMR ACQUISITION. Cine CMR was performed using a steady-state free precession sequence

FIGURE 2 Typical Examples of Patients With Advanced TR in Relation to Presence and Absence of NIsF



Representative examples of patients with advanced tricuspid regurgitation (TR), with and without NIsF. The arrow highlights NIsF. NIsF = nonischemic septal fibrosis; PA = pulmonary artery; RV = right ventricular; other abbreviations as in Figure 1.

(typical parameters: repetition time, 3.5 ms; echo time, 1.6 ms; flip angle, 60°; in-plane spatial resolution, 1.9 mm × 1.4 mm). Following cine CMR, gadolinium was intravenously administered (0.15-0.20 mmol/kg). Phase contrast CMR was acquired (typically postcontrast) for valvular flow assessment at the discretion of protocoling physicians or considering patient tolerance of additional breath-hold requirements. LGE CMR was initiated 10 minutes after gadolinium administration by using an inversion recovery sequence. Cine CMR and LGE CMR images were obtained in matching short- and long-axis planes. Short-axis images were acquired throughout the left ventricle (typically 6-mm slice thickness, 4-mm gap) from the mitral valve annulus through the apex. Long-axis images were acquired in standard 2-, 3- and 4-chamber orientations.

CMR ANALYSIS. **Tricuspid regurgitation.** All examinations were reviewed to exclude primary tricuspid valve disease. Advanced (≥ moderate) TR was evaluated quantitatively (on the basis of regurgitant volume [≥30 mL] and/or fraction [≥16%]).[12,13] In accordance with guidelines, regurgitant volume was assessed by differential forward stroke volume/RV stroke volume when phase contrast imaging of the pulmonic (or aortic) valve was available or through differential RV/left ventricular (LV) stroke volume when advanced mitral or aortic regurgitation was absent.[12]

Myocardial tissue characterization. The presence and extent of LGE were scored using an established semiquantitative protocol that was previously validated in relation to histopathologic features and clinical prognosis.[9,14,15] LGE localized using a 17-segment model, for which segments were graded on the basis of the transmural extent of hyperenhancement (0 = no hyperenhancement; 1 = 1%-25%; 2 = 26%-50%; 3 = 51%-75%; 4 = 76%-100%). Global infarct size (% LV myocardium) was calculated by summing all segmental scores (each weighted by the

TABLE 1 Demographic and Clinical Characteristics

	Overall (N = 663)	NIsF Absent (n = 468)	NIsF Present (n = 195)	*P* Value
Age, y	63.8 ± 16.0	64.0 ± 15.5	63.1 1 7.0	0.47
Male	349 (53)	228 (49)	121 (62)	**0.002**
BSA, m^2	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	0.24
Atherosclerosis risk factors				
Diabetes mellitus	154 (23)	115 (25)	39 (20)	0.21
Hypertension	436 (66)	309 (66)	127 (65)	0.80
Tobacco use	270 (42)	185 (41)	85 (44)	0.44
Hyperlipidemia	350 (53)	242 (52)	108 (56)	0.38
Family history (CAD)	218 (33)	159 (34)	59 (31)	0.35
CAD history				
Known CAD	303 (46)	209 (45)	94 (48)	0.44
Prior myocardial infarction	122 (18)	79 (17)	43 (22)	0.12
Prior revascularization	127 (19)	97 (21)	30 (16)	0.11
Cardiovascular medications				
Aspirin	254 (39)	194 (42)	60 (31)	**0.01**
HMG CoA-reductase inhibitor	305 (47)	213 (46)	92 (47)	0.78
Beta blocker	372 (57)	262 (57)	110 (57)	0.98
ACEI/ARB	249 (38)	179 (39)	70 (36)	0.51
Aldosterone antagonist	125 (19)	83 (18)	42 (22)	0.28
Loop diuretic agent	269 (41)	192 (42)	77 (40)	0.64
SGLT2 inhibitor	22 (3)	15 (3)	7 (4)	0.81
Sacubitril-valsartan	25 (4)	17 (4)	8 (4)	0.79
COPD	79 (12)	56 (12)	23 (12)	0.94
Atrial fibrillation	276 (42)	194 (42)	82 (42)	0.90
Prior CVA/TIA	76 (12)	54 (12)	22 (11)	0.91
Chronic kidney disease	95 (15)	67 (15)	28 (14)	0.99

Values are mean ± SD or n (%), unless otherwise indicated. **Bold** values indicate statistical significance ($P < 0.05$).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BSA = body surface area; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVA = cerebral vascular accident; HMG CoA = hydroxymethylglutaryl-coenzyme A; NIsF = nonischemic septal fibrosis; SGLT2 = sodium-glucose cotransporter 2; TIA = transient ischemic attack.

midpoint of range of hyperenhancement) and dividing by the total number of regions.[16]

LGE was also scored on the basis of pattern, including ischemic (subendocardial or transmural) or nonischemic (epicardial or midmyocardial) hyperenhancement. Regarding the latter, NIsF was defined as hyperenhancement within the midmyocardial and/or subepicardial aspects of the interventricular septum (**Figure 2**), including RV insertion points, in accordance with previous research by our group and others.[9-11]

Conventional remodeling indices. LV and RV chamber size and systolic function were quantified volumetrically on cine CMR. End-diastolic and end-systolic chamber volumes were quantified through endocardial border planimetry of contiguous short-axis images, with results used to calculate ejection fraction for each respective chamber; chamber dilation was determined in accordance with CMR guidelines.[17] Previous studies by our group[18,19] documented high reproducibility for both LV and RV quantitative analyses with methods used in this study. Cine CMR-quantified RV ejection fraction was used to define RV dysfunction on the basis of an established binary cutoff (<50%), as used in earlier research.[18,20]

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD (normally distributed data). Categorical variables are expressed as frequencies (percentages). Normally distributed continuous variables were compared using Student's *t*-tests (2-group comparisons) or analysis of variance (multiple group comparisons), and categorical variables were compared using chi-square tests. Variables known to affect TR outcomes were tested using univariable Cox proportional hazards analysis to identify associations with all-cause mortality. Those with significant univariable associations, along with variables of established clinical relevance, were considered for inclusion in the multivariable model while avoiding collinearity. A forward stepwise Cox proportional hazards model was used to test the incremental prognostic value of NIsF beyond conventional indices; incremental predictive utility was assessed on the basis of change in global chi-square values. Kaplan-Meier analysis was used to compare survival between groups (with and without NIsF). A 2-sided value of $P < 0.05$ was considered statistically significant. Statistical calculations were performed using SPSS software version 29.0 (IBM Corporation).

RESULTS

STUDY GROUP CHARACTERISTICS. The study cohort included 663 patients with advanced (≥ moderate) functional TR. Nearly one-third (29.4%) of these patients had NIsF identified on LGE CMR. All patients underwent comprehensive multiplanar cine CMR imaging, including contiguous short-axis data sets for quantifying RV function and volumes, as well as 4-chamber long-axis images to confirm the functional cause of TR.

Table 1 summarizes baseline demographic and clinical characteristics, including comparisons between patients with and without NIsF. As shown, a considerable proportion of patients had a history of cardiovascular comorbidities, inclusive of hypertension in two-thirds (66%) and clinically documented coronary artery disease in nearly one-half (46%) of the cohort. Regarding comparisons between groups, patients with NIsF were more likely to be male (62% vs 49%; $P = 0.002$) but showed no significant differences in the prevalence of remaining coronary artery disease risk factors.

CARDIAC CHAMBER GEOMETRY AND SYSTOLIC FUNCTION. Table 2 compares patients with and without NIsF with respect to left- and right-sided chamber geometry and function, as well as TR itself.[17] Regarding the left ventricle, patients with NIsF had increased LV size, greater LV mass, and decreased systolic function (all $P < 0.01$). Despite this, global LGE size was similar between groups ($P = 0.20$), a finding attributable to a lower extent of ischemic pattern LGE in patients with NIsF ($P < 0.001$).

Regarding right-sided structure and performance, patients with NIsF had significantly larger RV size and reduced systolic function (all $P < 0.001$), reflecting impaired RV adaptation and advanced remodeling. Additionally, NIsF was associated with greater TR severity, as evidenced by a higher tricuspid regurgitant volume and fraction among patients with NIsF compared with patients without NIsF (all $P < 0.001$).

Figure 3 stratifies TR severity and ventricular remodeling indices in relation to the presence and extent of NIsF. TR severity increased in relation to NIsF, as shown by stepwise increments in regurgitant fraction between groups partitioned on the basis of absence, localized (1 segment), and extensive (>1 segment) NIsF ($P < 0.001$). In parallel, RV size increase was 1.2-fold higher among patients with extensive NIsF as compared with patients without NIsF, thus paralleling similar stepwise associations for LV size (both $P < 0.001$).

CLINICAL PROGNOSIS. During a mean follow-up of 4.3 ± 4.3 years, overall mortality was 25.3% (168 deaths). Univariable Cox regression analyses (Table 3) identified several significant predictors of mortality, including advanced age (HR: 1.03 [95% CI: 1.02-1.05]; $P < 0.001$), RV dysfunction (HR: 1.69 [95% CI: 1.22-2.34]; $P = 0.002$), and RV dilation (HR: 1.66 [95% CI: 1.22-2.26]; $P = 0.001$). Mortality was nearly 1.5-fold higher in patients with NIsF compared with patients without NIsF (32% vs 23%; $P = 0.01$), with NIsF demonstrating a stronger association with mortality (HR: 1.80 [95% CI: 1.32-2.47]; $P < 0.001$) than ischemic pattern LGE (HR: 1.60 [95% CI: 1.16-2.19]; $P = 0.004$). TR severity, assessed on the basis of previously validated strata, and a regurgitant fraction ≥50%, identified as the highest-risk prognostic threshold,[21] were also predictors of all-cause mortality ($P < 0.05$ for all).

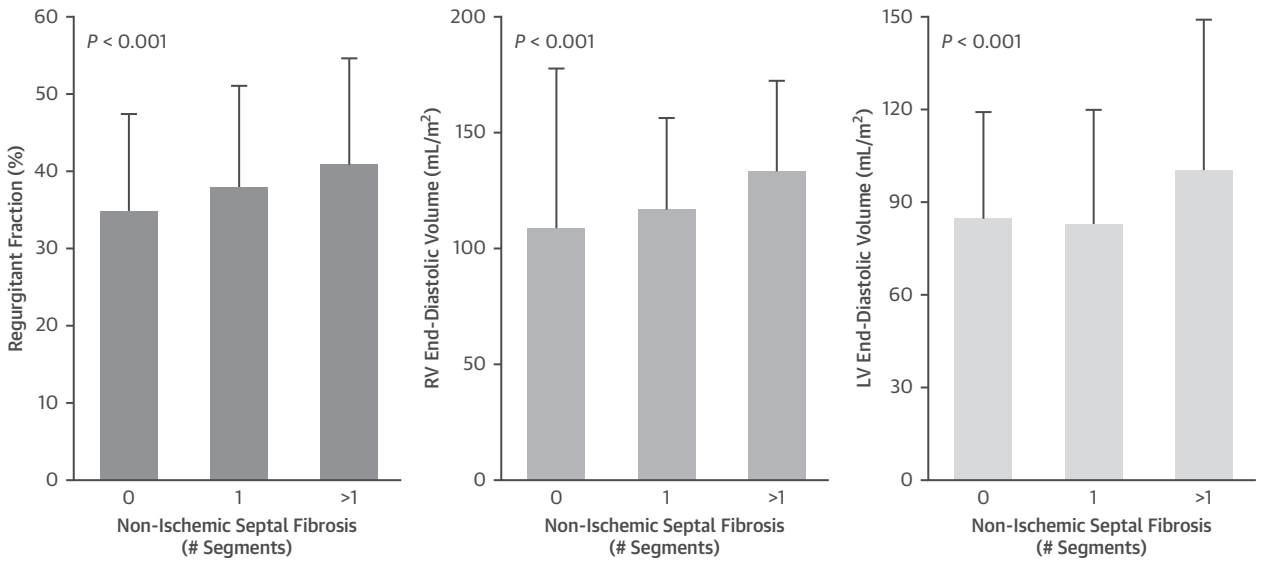
TABLE 2 Imaging Characteristics

	Overall (N = 663)	NIsF Absent (n = 468)	NIsF Present (n = 195)	*P* Value
LV geometry/function				
LV end-diastolic volume, mL/m^2	87.9 ± 38.6	84.8 ± 34.6	95.3 ± 46.0	**0.005**
LV end-systolic volume, mL/m^2	50.2 ± 38.3	46.2 ± 34.1	59.7 ± 45.5	**<0.001**
LV myocardial mass, g/m^2	70.3 ± 25.4	68.3 ± 24.0	75.0 ± 28.0	**0.005**
LV ejection fraction, %	48.6 ± 18.7	50.2 ± 18.0	44.8 ± 19.9	**0.001**
LV dilation[a]	180 (27)	107 (23)	73 (37)	**<0.001**
LV dysfunction[b]	302 (46)	197 (42)	105 (54)	**0.01**
RV geometry/function				
RV end-diastolic volume, mL/m^2	112.8 ± 37.3	106.1 ± 34.1	129.0 ± 39.7	**<0.001**
RV end-systolic volume, mL/m^2	64.2 ± 31.4	57.4 ± 27.4	80.5 ± 34.4	**<0.001**
RV ejection fraction, %	45.2 ± 12.2	47.6 ± 11.5	39.6 ± 12.2	**<0.001**
RV dilation[c]	352 (53)	214 (46)	138 (71)	**<0.001**
RV dysfunction[d]	403 (61)	245 (52)	158 (81)	**<0.001**
Tricuspid regurgitation				
TR volume, mL	33.1 ± 18.0	31.4 ± 17.0	37.1 ± 19.8	**<0.001**
TR fraction, %	36.4 ± 13.0	34.9 ± 12.5	40.1 ± 13.6	**<0.001**
Right atrial area, cm^2	30.5 ± 11.0	29.2 ± 10.0	33.2 ± 12.3	**<0.001**
Mitral regurgitation				
Advanced MR, ≥ moderate	236 (36)	159 (34)	77 (40)	0.18
Left atrial dimension, cm	4.3 ± 2.5	4.3 ± 2.8	4.3 ± 1.1	0.97
Left atrial area, cm^2	28.2 ± 10.8	27.9 ± 10.4	29.1 ± 11.7	0.23
LV tissue characterization				
Global hyperenhancement size, % LV	4.6 ± 8.8	4.9 ± 9.8	4.1 ± 5.6	0.20
Ischemic scar/infarction (presence)	178 (27)	145 (31)	33 (17)	**<0.001**
Ischemic scar/infarction, No. segments	1.4 ± 2.9	1.7 ± 3.3	0.6 ± 1.8	**<0.001**
Nonischemic septal fibrosis, No. segments	0.7 ± 1.2	0.0 ± 0.0	2.3 ± 1.2	**<0.001**

Values are mean ± SD or n (%), unless otherwise indicated. **Bold** values indicate statistical significance ($P < 0.05$). [a]LV end-diastolic volume index >108 mL/m^2 for men and >96 mL/m^2 for women.[17] [b]LV ejection fraction <50%. [c]RV end-diastolic volume index >109 mL/m^2 for men and >97 ml/m^2 for women.[17] [d]RV ejection fraction <50%.

LV = left ventricular; MR = mitral regurgitation; RV = right ventricular; TR = tricuspid regurgitation; other abbreviation as in Table 1.

FIGURE 3 Impact of NIsF on Chamber Remodeling and TR Severity



Bar graphs illustrating the relationship between NIsF and conventional risk markers in TR, showing a stepwise increase in NIsF burden corresponding to greater chamber remodeling and TR severity. LV = left ventricular; other abbreviations as in Figure 2.

Multivariable Cox regression analysis (Table 3), incorporating variables with established clinical relevance and significant univariable associations, demonstrated NIsF to predict mortality independently (HR: 1.79 [95% CI: 1.26-2.56]; $P = 0.001$), even after adjustment for age, RV dysfunction, RV dilation, and TR severity. Among these factors, age (HR: 1.04 [95% CI: 1.03-1.05]; $P < 0.001$) and RV dilation (HR: 1.55 [95% CI: 1.12-2.16]; $P = 0.01$) remained significant predictors in the multivariable model. Notably, RV dysfunction did not achieve statistical significance (HR: 1.27 [95% CI: 0.86-1.87]; $P = 0.24$), a finding highlighting the incremental prognostic value of NIsF, which may capture advanced myocardial disease and remodeling not fully reflected by traditional RV functional indices. Additional Cox regression analysis was performed in 424 patients with a TR regurgitant fraction ≥30%;[21,22] in these patients, NIsF remained strongly associated with all-cause mortality in both univariate and multivariate analyses (Supplemental Table 1).

The incremental prognostic value of NIsF was demonstrated through sequential improvements in model performance, reflected by increasing chi-square values with the addition of each prognostic factor. Age was independently associated with mortality and produced a chi-square value of 33.9 ($P < 0.001$). Adding RV and LV ejection fraction significantly improved the model (chi-square = 49.6; $P = 0.006$), followed by the inclusion of RV end-diastolic volume index (chi-square = 57.8; $P = 0.003$), factors highlighting the importance of functional and volumetric RV parameters for risk stratification in TR. The model also improved after the inclusion of TR severity (chi-square = 62.3; $P = 0.04$). The inclusion of ischemic scar/infarction further enhanced the model (chi-square = 65.6; $P = 0.06$). Notably, the addition of NIsF resulted in the greatest improvement (chi-square = 76.9; $P = 0.001$), highlighting the incremental prognostic value of NIsF beyond traditional clinical and imaging parameters.

Figure 4 provides Kaplan-Meier survival curves among patients grouped on the basis of the presence or absence of NIsF. As shown, overall survival was lower among patients with NIsF compared with those without NIsF (log-rank $P < 0.001$).

DISCUSSION

This study offers novel insights into the prognostic significance of NIsF in patients with functional TR (**Central Illustration**). Our findings demonstrate that NIsF detected on LGE CMR is not only highly prevalent, affecting more than one-fourth of the study patients but also strongly associated with increased all-cause mortality risk, even after adjusting for conventional risk factors, including age and RV remodeling. Additionally, our data reveal that NIsF is independently associated with markers of RV dysfunction, thereby highlighting its potential role as a mediator of adverse RV remodeling in TR. These findings emphasize the importance of myocardial tissue characterization in understanding the mechanisms and clinical implications of right-sided heart adaptations in TR.

Our results build on previous mechanistic research suggesting that NIsF reflects maladaptive remodeling driven by increased afterload and wall stress.[23-25] Functional TR is marked by elevated RV volume and pressure overload, which drive progressive dilation and dysfunction of the right ventricle and, indirectly, the left ventricle. The interventricular septum, subjected to mechanical strain from both ventricles, has been shown to be particularly vulnerable to fibrosis.[26-28] Unlike the circumferential fibers of the RV free wall, the longitudinally oriented myofibrils in the septum are highly susceptible to disruptions in contractility, which can significantly impair RV function.[7,29] Septal fibrosis increases myocardial stiffness, limits RV compliance and diastolic filling, and ultimately contributes to reduced stroke volume and overall cardiac output.[30] Furthermore, septal fibrosis restricts septal movement, which impairs ventricular interdependence and exacerbates wall stress.[8,31] Experimental murine models have shown such strain to drive myocardial remodeling and fibrosis formation further, establishing a cycle of adverse structural changes.[32] Altogether, our findings and previous literature suggest that NIsF may serve as both a consequence of and a contributor to adverse remodeling in TR, thus highlighting its potential role in the progression of right-sided heart failure.

Our study is the first, to our knowledge, to demonstrate the incremental prognostic value of NIsF beyond traditional imaging parameters such as RV alterations and TR severity. Although RV dysfunction has long been recognized as a critical marker of

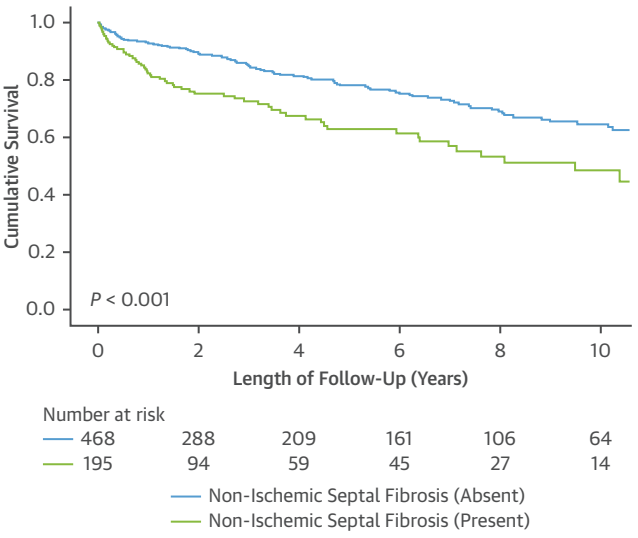
TABLE 3 Univariable and Multivariable Cox Regression Analysis for Mortality

	HR	95% CI	*P* Value
Univariable mortality analysis			
Demographic and clinical characteristics			
Male	0.92	0.68-1.25	0.59
Age	1.03	1.02-1.05	**<0.001**
Hypertension	0.89	0.65-1.21	0.45
Hypercholesterolemia	0.88	0.65-1.20	0.43
Diabetes mellitus	0.96	0.67-1.37	0.82
Prior myocardial infarction	1.46	1.02-2.07	**0.04**
Known CAD	1.12	0.82-1.51	0.48
LV geometry/function			
LV dilation[a]	1.32	0.95-1.83	0.10
LV dysfunction[b]	1.47	1.08-1.99	**0.01**
RV geometry/function			
RV dilation[c]	1.66	1.22-2.26	**0.001**
RV dysfunction[d]	1.69	1.22-2.34	**0.002**
Tricuspid regurgitation			
TR regurgitant volume strata[e]	1.24	1.01-1.51	**0.04**
TR regurgitant fraction strata[f]	1.30	1.05-1.62	**0.02**
TR regurgitant fraction ≥50%	1.69	1.17-2.45	**0.01**
LV tissue characterization			
Global hyperenhancement size (%LV)	1.02	1.01-1.04	**0.004**
Ischemic scar/infarction (presence)	1.60	1.16-2.19	**0.004**
Ischemic scar/infarction (#segments)	1.09	1.04-1.14	**<0.001**
NIsF (presence)	1.80	1.32-2.47	**<0.001**
NIsF (#segments)	1.18	1.06-1.31	**0.002**
Multivariable mortality analysis (chi-square = 76.9, $P < 0.001$)			
Age	1.04	1.03-1.05	**<0.001**
RV dysfunction[d]	1.27	0.86-1.87	0.24
LV dysfunction[b]	1.05	0.72-1.52	0.80
RV dilation[c]	1.55	1.12-2.16	**0.01**
TR regurgitant fraction ≥50%	1.42	0.96-2.08	0.08
NIsF (presence)	1.79	1.26-2.56	**0.001**
Ischemic scar/infarction (presence)	1.63	1.13-2.36	**0.01**

Bold indicates statistical significance ($P < 0.05$). [a]LVEDVi >108 mL/m^2 for men and LVEDVi >96 mL/m^2 for women.[17] [b]LVEF <50%. [c]RVEDVi >109 mL/m^2 for men and RVEDVi >97 mL/m^2 for women.[17] [d]RVEF <50%. [e]Regurgitant volume <30 mL, 30-44 mL, ≥45 mL.[21] [f]Regurgitant fraction <30%, 30-49%, ≥50%.[21]

LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; other abbreviations as in **Tables 1 and 2**.

FIGURE 4 Kaplan-Meier Survival Curve Stratified By NIsF



Kaplan-Meier survival curve in patients with advanced functional TR depicting increased all-cause mortality risk when stratified by NIsF ($P < 0.001$). Abbreviations as in Figure 2.

adverse outcomes in TR,[33-35] our findings suggest that NIsF provides unique prognostic information that extends beyond conventional metrics. Notably, in multivariable analysis, NIsF emerged as an independent predictor of mortality, whereas RV dysfunction did not. These findings suggest that NIsF may capture distinct and potentially more advanced aspects of myocardial disease not adequately reflected in conventional RV volumetric and functional assessments. Regarding TR itself, although TR severity is a known determinant of outcomes,[21,22,36] our study findings suggest that myocardial tissue alterations may provide complementary prognostic information by capturing the impact of RV maladaptive remodeling. This is particularly relevant given that RV function and TR severity are dynamic and influenced by loading conditions, whereas myocardial fibrosis may represent a more stable marker of advanced disease. These findings reinforce the potential role of myocardial tissue characterization in understanding the mechanisms and clinical implications of right-sided heart adaptations in TR.

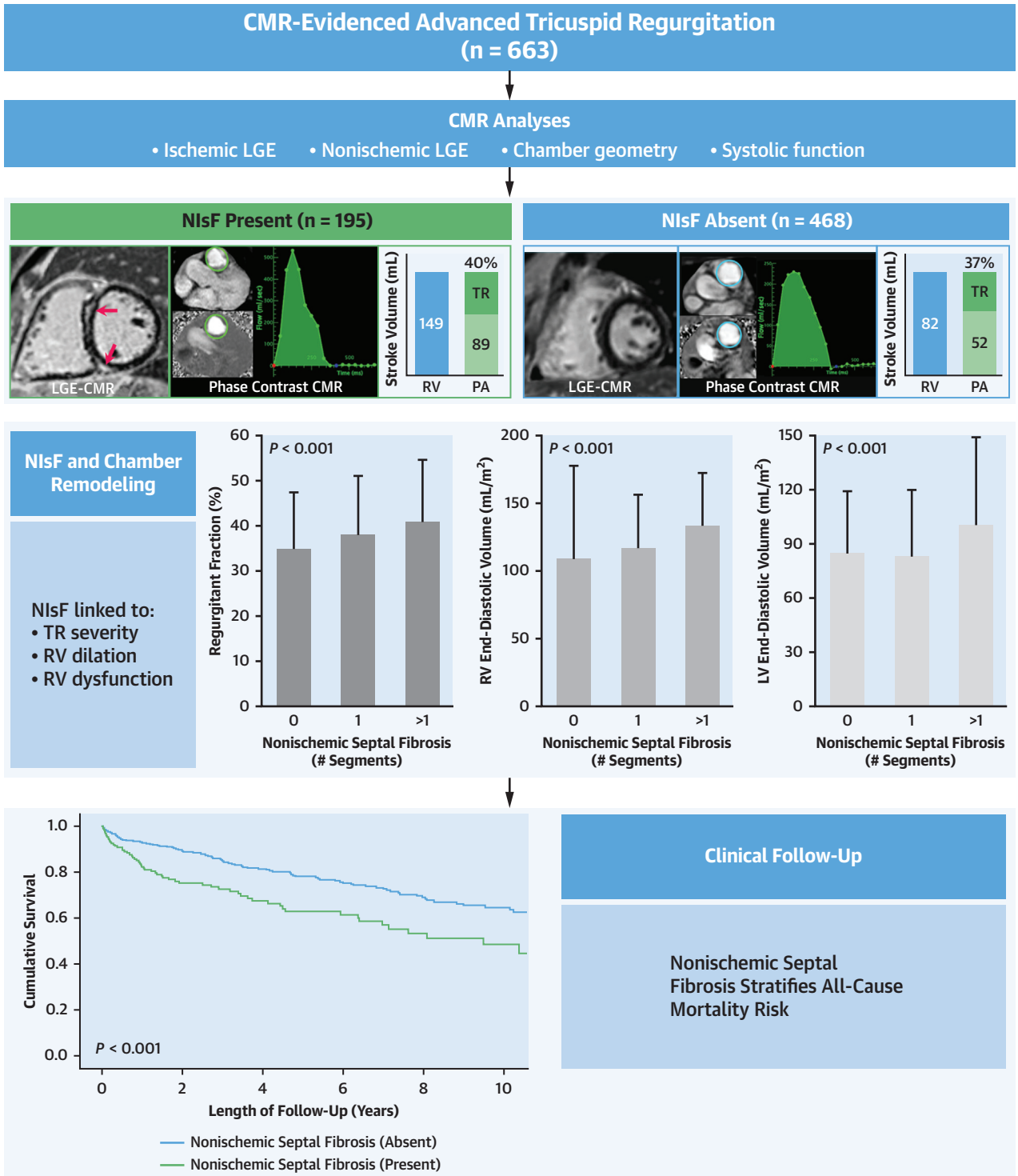
From a clinical perspective, NIsF detection on LGE CMR could have important implications for the management of patients with functional TR. Identifying NIsF early in the course of TR may allow for more aggressive therapeutic interventions, such as optimized medical therapy, closer clinical monitoring, or earlier consideration of percutaneous or surgical intervention. Moreover, incorporating NIsF into clinical decision-making algorithms could improve the timing of interventions, thus potentially improving long-term outcomes in these high-risk patients toward the goal of mitigating the progression of heart failure and other associated adverse clinical outcomes.

STUDY LIMITATIONS. Although our findings are promising, several limitations should be acknowledged. We demonstrate the prognostic significance of NIsF in patients with TR, but the mechanisms driving the development and progression of septal fibrosis in this setting remain to be fully elucidated. Increased RV afterload and wall stress are thought to contribute to septal fibrosis, but the specific pathophysiological pathways and cellular responses involved are not yet completely understood. Furthermore, although the study included a well-characterized cohort with advanced functional TR, its retrospective, single-center design and lack of serial imaging data may limit generalizability and prevent assessment of dynamic changes in septal fibrosis and cardiac remodeling over time. Additionally, even though we performed TR quantification using established methods, the absence of uniform pulmonary velocity-encoded phase-contrast imaging presents a limitation; nonetheless, our findings demonstrate a prognostic association.

CONCLUSIONS

This study demonstrates that among patients with advanced TR, myocardial injury (NIsF) noted on LGE CMR is strongly associated with adverse right-sided chamber remodeling and provides incremental prognostic utility beyond conventional risk factors. Study findings highlight the importance of myocardial tissue characterization in patients with functional TR and lay the foundation for future research to test whether targeted interventions can improve outcomes.

CENTRAL ILLUSTRATION **Nonischemic Septal Fibrosis as a Marker for Tricuspid Regurgitation Severity, Right Ventricular Remodeling, and Mortality Risk**



Villar-Calle P, et al. JACC Cardiovasc Imaging. 2025;■(■):■-■.

(Top) Study group of 663 patients with advanced tricuspid regurgitation (TR) undergoing comprehensive cardiac magnetic resonance (CMR) analysis. (Middle) Representative examples of nonischemic septal fibrosis (NIsF) on late gadolinium enhancement (LGE)-CMR. NIsF is strongly associated with TR severity and right ventricular (RV) remodeling. (Bottom) Kaplan-Meier survival curve demonstrating NIsF to stratify all-cause mortality risk. LV = left ventricular; PA = pulmonary artery.

DATA AVAILABILITY. Data, analytic methods, and study materials can be made available for result reproduction or procedure replication on reasonable request.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: NIsF detected by LGE-CMR is prevalent in patients with advanced functional tricuspid regurgitation and represents an important marker of adverse right-sided chamber remodeling. NIsF provides incremental prognostic value for all-cause mortality beyond conventional imaging parameters including right ventricular dysfunction and dilation.

TRANSLATIONAL OUTLOOK: Future studies are needed to discern mechanisms of septal fibrosis development and progression in tricuspid regurgitation and test its role as a risk stratification tool and therapeutic target through serial imaging and intervention studies.

REFERENCES

1. Neuhold S, Huelsmann M, Pernicka E, et al. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. *Eur Heart J*. 2013;34:844–852. https://doi.org/10.1093/eurheartj/ehs465

2. Lindman BR, Maniar HS, Jaber WA, et al. Effect of tricuspid regurgitation and the right heart on survival after transcatheter aortic valve replacement: insights from the Placement of Aortic Transcatheter Valves II inoperable cohort. *Circ Cardiovasc Interv*. 2015;8:e002073. https://doi.org/10.1161/CIRCINTERVENTIONS.114.002073

3. Agricola E, Marini C, Stella S, et al. Effects of functional tricuspid regurgitation on renal function and long-term prognosis in patients with heart failure. *J Cardiovasc Med (Hagerstown)*. 2017;18:60–68. https://doi.org/10.2459/JCM.0000000000000312

4. Kochav JD, Kim J, Judd R, et al. Myocardial contractile mechanics in ischemic mitral regurgitation: multicenter data using stress perfusion cardiovascular magnetic resonance. *JACC Cardiovasc Imaging*. 2022;15:1212–1226. https://doi.org/10.1016/j.jcmg.2022.03.014

5. Kochav JD, Kim J, Judd R, et al. Ischemia-mediated dysfunction in subpapillary myocardium as a marker of functional mitral regurgitation. *JACC Cardiovasc Imaging*. 2021;14:826–839. https://doi.org/10.1016/j.jcmg.2021.01.007

6. Cavalcante JL, Kusunose K, Obuchowski NA, et al. Prognostic impact of ischemic mitral regurgitation severity and myocardial infarct quantification by cardiovascular magnetic resonance. *JACC Cardiovasc Imaging*. 2020;13:1489–1501. https://doi.org/10.1016/j.jcmg.2019.11.008

7. Buckberg G, Hoffman JI. Right ventricular architecture responsible for mechanical performance: unifying role of ventricular septum. 2014. *J Thorac Cardiovasc Surg*. 2014;148:3166–3171. e3161-3164 https://doi.org/10.1016/j.jtcvs.2014.05.044

8. Nguyen-Truong M, Liu W, Doherty C, et al. The interventricular septum is biomechanically distinct from the ventricular free walls. *Bioengineering (Basel)*. 2021;8(12):216. https://doi.org/10.3390/bioengineering8120216

9. Gulati A, Jabbour A, Ismail TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA*. 2013;309:896–908. https://doi.org/10.1001/jama.2013.1363

10. Kim J, Medicherla CB, Ma CL, et al. Association of right ventricular pressure and volume overload with non-ischemic septal fibrosis on cardiac magnetic resonance. *PLoS One*. 2016;11:e0147349.

11. Freed BH, Gomberg-Maitland M, Chandra S, et al. Late gadolinium enhancement cardiovascular magnetic resonance predicts clinical worsening in patients with pulmonary hypertension. *J Cardiovasc Magn Reson*. 2012;14:11. https://doi.org/10.1186/1532-429X-14-11

12. 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;30:303–371. https://doi.org/10.1016/j.echo.2017.01.007

13. Hahn RT, Thomas JD, Khalique OK, Cavalcante JL, Praz F, Zoghbi WA. Imaging assessment of tricuspid regurgitation severity. *JACC Cardiovasc Imaging*. 2019;12:469–490. https://doi.org/10.1016/j.jcmg.2018.07.033

14. Purmah Y, Cornhill A, Lei LY, et al. Mid-wall striae fibrosis predicts heart failure admission, composite heart failure events, and life-threatening arrhythmias in dilated cardiomyopathy. *Sci Rep*. 2022;12:1739. https://doi.org/10.1038/s41598-022-05790-y

15. Alba AC, Gaztanaga J, Foroutan F, et al. Prognostic value of late gadolinium enhancement for the prediction of cardiovascular outcomes in dilated cardiomyopathy: an international, multi-institutional study of the MINICOR Group. *Circ Cardiovasc Imaging*. 2020;13:e010105. https://doi.org/10.1161/CIRCIMAGING.119.010105

16. Sievers B, Elliott MD, Hurwitz LM, et al. Rapid detection of myocardial infarction by subsecond, free-breathing delayed contrast-enhancement cardiovascular magnetic resonance. *Circulation*. 2007;115:236–244. https://doi.org/10.1161/CIRCULATIONAHA.106.635409

17. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, et al. Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. *J Cardiovasc Magn Reson*. 2020;22:87. https://doi.org/10.1186/s12968-020-00683-3

18. Kim J, Srinivasan A, Seoane T, et al. Echocardiographic linear dimensions for assessment of right ventricular chamber volume as demonstrated by cardiac magnetic resonance. *J Am Soc Echocardiogr*. 2016;29:861–870. https://doi.org/10.1016/j.echo.2016.05.002

19. Kochav J, Chen J, Nambiar L, et al. Novel echocardiographic algorithm for right ventricular mass quantification: cardiovascular magnetic resonance and clinical prognosis validation. *J Am Soc Echocardiogr*. 2021;34:839–850.e831. https://doi.org/10.1016/j.echo.2021.03.002

20. Villar-Calle P, Kochav JD, Vadaketh K, et al. Tissue-based predictors of impaired right ventricular strain in coronary artery disease: a multicenter stress perfusion study. *Circ Cardiovasc Imaging*. 2024;17:e016852. https://doi.org/10.1161/CIRCIMAGING.124.016852

21. Zhan Y, Debs D, Khan MA, et al. Natural history of functional tricuspid regurgitation quantified by cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2020;76:1291-1301. https://doi.org/10.1016/j.jacc.2020.07.036

22. Wang TKM, Akyuz K, Reyaldeen R, et al. Prognostic value of complementary echocardiography and magnetic resonance imaging quantitative evaluation for isolated tricuspid regurgitation. *Circ Cardiovasc Imaging*. 2021;14:e012211. https://doi.org/10.1161/circimaging.120.012211

23. Iyer NR, Le TT, Kui MSL, et al. Markers of focal and diffuse nonischemic myocardial fibrosis are associated with adverse cardiac remodeling and prognosis in patients with hypertension: the REMODEL study. *Hypertension*. 2022;79:1804-1813. https://doi.org/10.1161/HYPERTENSIONAHA.122.19225

24. Andersen S, Nielsen-Kudsk JE, Vonk Noordegraaf A, de Man FS. Right ventricular fibrosis. *Circulation*. 2019;139:269-285. https://doi.org/10.1161/CIRCULATIONAHA.118.035326

25. Alter P, Rupp H, Adams P, et al. Occurrence of late gadolinium enhancement is associated with increased left ventricular wall stress and mass in patients with non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail*. 2011;13:937-944. https://doi.org/10.1093/eurjhf/hfr082

26. Friedberg MK. Imaging right-left ventricular interactions. *JACC Cardiovasc Imaging*. 2018;11:755-771. https://doi.org/10.1016/j.jcmg.2018.01.028

27. Csecs I, Pashakhanloo F, Paskavitz A, et al. Association between left ventricular mechanical deformation and myocardial fibrosis in nonischemic cardiomyopathy. *J Am Heart Assoc*. 2020;9:e016797. https://doi.org/10.1161/JAHA.120.016797

28. Sanz J, Dellegrottaglie S, Kariisa M, et al. Prevalence and correlates of septal delayed contrast enhancement in patients with pulmonary hypertension. *Am J Cardiol*. 2007;100:731-735. https://doi.org/10.1016/j.amjcard.2007.03.094

29. Houston BA, Brittain EL, Tedford RJ. Right ventricular failure. *N Engl J Med*. 2023;388:1111-1125. https://doi.org/10.1056/NEJMra2207410

30. Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. Cardiac fibrosis: the fibroblast awakens. *Circ Res*. 2016;118:1021-1040. https://doi.org/10.1161/CIRCRESAHA.115.306565

31. Naeije R, Badagliacca R. The overloaded right heart and ventricular interdependence. *Cardiovasc Res*. 2017;113:1474-1485. https://doi.org/10.1093/cvr/cvx160

32. Reddy S, Zhao M, Hu DQ, et al. Physiologic and molecular characterization of a murine model of right ventricular volume overload. *Am J Physiol Heart Circ Physiol*. 2013;304:H1314-H1327. https://doi.org/10.1152/ajpheart.00776.2012

33. Dietz MF, Prihadi EA, van der Bijl P, et al. prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation. *Circulation*. 2019;140:836-845. https://doi.org/10.1161/CIRCULATIONAHA.119.039630

34. Bombace S, Fortuni F, Viggiani G, et al. Right heart remodeling and outcomes in patients with tricuspid regurgitation: a literature review and meta-analysis. *JACC Cardiovasc Imaging*. 2024;17:595-606. https://doi.org/10.1016/j.jcmg.2023.12.011

35. Ogawa M, Kuwajima K, Yamane T, Hasegawa H, Yagi N, Shiota T. Prognostic implication of right ventricular free wall longitudinal strain and right atrial pressure estimated by echocardiography in patients with severe functional tricuspid regurgitation. *J Am Heart Assoc*. 2024;13:e033196. https://doi.org/10.1161/JAHA.123.033196

36. Seo J, Hong YJ, Batbayar U, et al. Prognostic value of functional tricuspid regurgitation quantified by cardiac magnetic resonance in heart failure. *Eur Heart J Cardiovasc Imaging*. 2023;24:742-750. https://doi.org/10.1093/ehjci/jeac224

KEY WORDS cardiac magnetic resonance, nonischemic fibrosis, prognostic marker, tricuspid regurgitation

APPENDIX For a supplemental table, please see the online version of this paper.