JACC: CARDIOVASCULAR IMAGING VOL. 14, NO. 8, 2021
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ORIGINAL RESEARCH

Prognostic Value of Feature-Tracking Right Ventricular Longitudinal Strain in Severe Functional Tricuspid Regurgitation

A Multicenter Study

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ABSTRACT

OBJECTIVES This study sought to evaluate the prognostic value of cardiac magnetic resonance (CMR) feature-tracking–derived right ventricular (RV) free wall longitudinal strain (RVFWLS) in a large multicenter population of patients with severe functional tricuspid regurgitation.

BACKGROUND Tricuspid regurgitation imposes a volume overload on the RV that can lead to progressive RV dilation and dysfunction. Overt RV dysfunction is associated with poor prognosis and increased operative risk. Abnormalities of myocardial strain may provide the earliest evidence of ventricular dysfunction. CMR feature-tracking techniques now allow assessment of strain from routine cine images, without specialized pulse sequences. Whether abnormalities of RV strain measured using CMR feature tracking have prognostic value in patients with tricuspid regurgitation is unknown.

METHODS Consecutive patients with severe functional tricuspid regurgitation undergoing CMR at 4 U.S. medical centers were included in this study. Feature-tracking RVFWLS was calculated from 4-chamber cine views. The primary endpoint was all-cause death. Cox proportional hazards regression modeling was used to examine the independent association between RVFWLS and death. The incremental prognostic value of RVFWLS was assessed in nested models.

RESULTS Of the 544 patients in this study, 128 died during a median follow-up of 6 years. By Kaplan-Meier analysis, patients with RVFWLS ≥median (−16%) had significantly reduced event-free survival compared with those with RVFWLS <median (log-rank $p < 0.001$). By Cox multivariable regression modeling, RVFWLS was associated with increased risk-of-death after adjustment for clinical and imaging risk factors, including RV size and ejection fraction (hazard ratio: 1.14 per %; $p < 0.001$). Addition of RVFWLS in this model resulted in significant improvement in the global chi-square (31 to 78; $p < 0.001$).

CONCLUSIONS CMR feature-tracking–derived RVFWLS is an independent predictor of mortality in patients with severe functional tricuspid regurgitation, incremental to common clinical and imaging risk factors.
(J Am Coll Cardiol Img 2021;14:1561–8) © 2021 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 16, 2020; revised manuscript received January 25, 2021, accepted February 5, 2021.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2021.02.009

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

CMR = cardiac magnetic resonance

EF = ejection fraction

LGE = late gadolinium enhancement

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

RV = right ventricle/ventricular

RVEDV = right ventricular end-diastolic volume

RVEF = right ventricular ejection fraction

RVFWLS = right ventricular free wall longitudinal strain

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

Severe tricuspid regurgitation (TR) is associated with poor prognosis (1–5). However, compared with mitral or aortic disease, the natural history and underlying pathophysiology of TR and its relationship to right ventricular (RV) function is less understood (6). There is also incomplete knowledge on the role and timing of tricuspid valve surgery and newer transcatheter repair approaches (6–8). Better understanding of underlying mechanisms and prognostic assessment of TR is essential for developing adequate and timely treatments. It is known that severe TR imposes a volume overload on the ventricle that can lead to progressive RV dilation and dysfunction (2,6,9). Overt RV dysfunction is associated with poor prognosis and increased operative risk (2,7,10). However, patients with severe TR are a heterogeneous population at different stages of right heart modeling (11).

Abnormalities of myocardial strain may provide the earliest evidence of RV dysfunction (12). Cardiac magnetic resonance (CMR) feature-tracking techniques now allow assessment of strain from routine cine images, without specialized pulse sequences (13). CMR also allows accurate assessment of RV function and size. Whether abnormalities of RV strain measured using CMR feature tracking have prognostic value in patients with severe TR is unknown. We hypothesized that feature-tracking-derived RV longitudinal strain (RVFWLS) may provide prognostic information incremental to clinical and standard CMR-derived parameters in this patient group.

The aim of this study was to evaluate the prognostic value of CMR feature-tracking-derived RVFWLS in a large multicenter population of patients with severe functional TR.

METHODS

STUDY DESIGN. Four geographically diverse medical centers in the United States participated in this retrospective, observational, multicenter study. The University of Illinois in Chicago served as the data-coordinating center using a cloud-based database (CloudCMR, Heart Imaging Technologies, Durham, North Carolina) containing deidentified searchable data from consecutive patients with full DICOM datasets from the participating centers. Institutional review board approval was obtained at each center.

STUDY POPULATION. In this retrospective study, consecutive patients with clinically reported severe TR who had undergone CMR with both cine and late gadolinium enhancement (LGE) imaging formed the study population of 544 patients. Severe TR was assessed by an experienced level 3 CMR reader with a qualitative multiparametric integrative approach based on a combination of right atrial enlargement, lack of leaflet coaptation, vena contracta >7 mm, signal void area >50% of the right atrium, RV enlargement, and tricuspid annular dilatation (14–17). Exclusion criteria included tricuspid valve prolapse, endocarditis, tumor, as well as pacemaker or congenital heart disease. Baseline demographics (age, sex, body mass index, history of diabetes, history of hyperlipidemia, history of hypertension, history of smoking, history of pulmonary hypertension, cardiac medications) were obtained by local site investigators at the time of the clinical study. History of diabetes, history of hyperlipidemia, history of hypertension, history of smoking, and history of pulmonary hypertension were assessed based on documentation of the diagnosis in the electronic medical record at the time of the CMR exam.

CMR ACQUISITION. Images were acquired with phased-array receiver coils according to the routine scan protocol at each site using a variety of scanners from all 3 major vendors (Siemens, Munich, Germany; Philips, Amsterdam, the Netherlands; and General Electric, Boston, Massachusetts) at both 1.5 and 3 Tesla. A typical protocol included steady-state free-precession cine images acquired in multiple short-axis and 3 long-axis views (left ventricular [LV] 4-, 2-, and 3-chamber) with short-axis views obtained every 1 cm to cover the entire LV (18). Typical temporal resolution of cine images was <45 ms. LGE imaging was performed 10 to 15 min after gadolinium contrast (0.15 mmol/kg) administration using a 2-dimensional (2D) segmented gradient echo inversion-recovery sequence in the same views used for cine CMR. Inversion delay times were typically 280 to 360 ms.

CMR ANALYSIS AND RVFWLS ASSESSMENT. The study site investigators analyzed images on locally available workstations and were blinded to follow-up data. LV and RV volumes and ejection fractions (EFs), as well as LV mass, were determined by quantitative analysis according to Society of Cardiovascular Magnetic Resonance recommendations (18). Right atrial area was measured in the cine 4-chamber view, just before tricuspid valve opening. Tricuspid annular plane systolic excursion (TAPSE) was measured from cine CMR images. As previously described, the presence of LGE was determined by visual inspection on a 17-segment model per standardized Society of Cardiovascular Magnetic

Resonance recommendations (18–25). For feature-tracking analysis, endocardial RV contours were manually traced (by a single physician [S.R.] who was blinded to patient information and outcomes) in the long-axis 4-chamber cine view to derive RVFWLS using Segment CMR software (Medviso AB, Lund, Sweden) (**Figure 1**). In 50 randomly selected patients, a blinded CMR physician measured RVFWLS for assessment of interobserver variability.

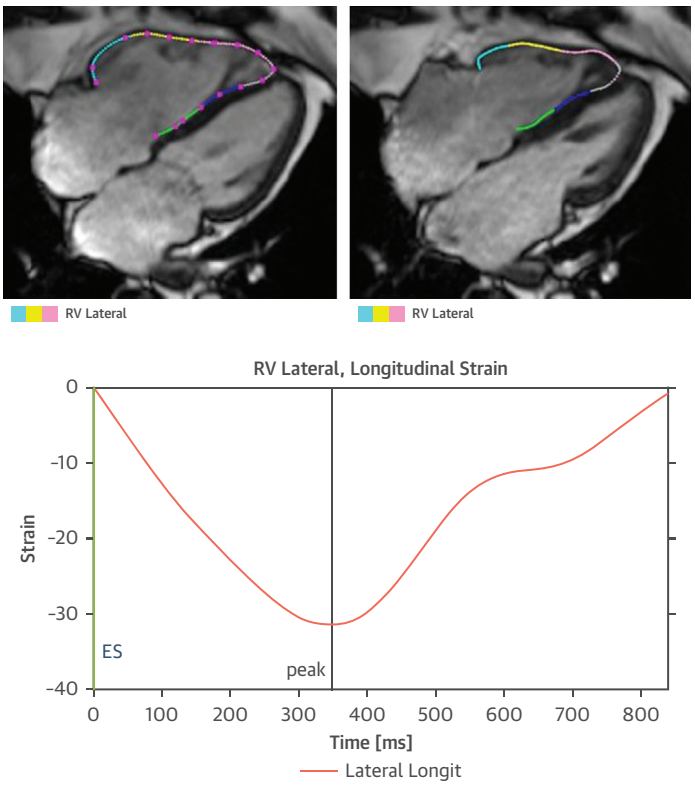
FOLLOW-UP. Patients were followed for the primary outcome of all-cause mortality using the U.S. Social Security Death Index. Time to event was calculated as the period between the CMR study and death. Patients who did not experience the primary outcome were censored at the time of assessment.

STATISTICAL ANALYSIS. Normally distributed data were expressed as mean ± SD. Differences in baseline characteristics were compared with the Student's *t*-test for continuous variables and the chi-square test for dichotomous variables. Interobserver variability for RVFWLS was assessed in a random sample of 50 patients using the Bland-Altman method. Kaplan-Meier methods were used to evaluate the relationship between RVFWLS and time to the primary outcome of all-cause mortality. A cubic spline model was fitted to the observed data to illustrate the association between RVFWLS as a continuous variable and outcome. We used Cox proportional hazards regression modeling to examine the association between RVFWLS and all-cause mortality. All models were assessed for collinearity and proportional hazards assumption. For the multivariable models, established important clinical and imaging risk factors based on prior prognostic published reports were considered as covariates: age, sex, diabetes, hypertension, pulmonary hypertension, left-sided valve disease, LV ejection fraction (LVEF), LGE, TAPSE, RV end-diastolic volume (RVEDV), RV ejection fraction (RVEF) (3,11,26). The incremental prognostic value of RVFWLS was assessed in nested models. A p value of <0.05 was considered statistically significant. Analyses were performed using STATA software (StataCorp, College Station, Texas).

RESULTS

PATIENT CHARACTERISTICS. **Table 1** summarizes baseline patient characteristics stratified by RVFWLS above and below the median (−16%). The mean age of the study population was 60.6 ± 18.6 years. Forty-one percent of patients were male, and 16.5% had diabetes mellitus. History of pulmonary hypertension was present in 14.3%, whereas 42% had moderate or more left-sided valve disease. The mean RVEF was 37%. The mean LVEF was 52.4 ± 15.5%, and LGE was present in 36.6% of patients. The mean TAPSE was 14 mm. Scatter plots in Supplemental Figures 1 to 3 show the correlations between: 1) RVFWLS and RVEF; 2) RVFWLS and RVEDV; and 3) RVFWLS and LVEF. Bland-Altman analysis of interobserver variability for RVFWLS showed a bias of 0.19%. The 95% limits of agreement were −2% to 1.66% (Supplemental Figure 4).

FIGURE 1 Measurement of RVFWLS Using the Segment CMR Package



Endocardial right ventricular (RV) contours were manually traced in the 4-chamber cine view to derive the RV free wall longitudinal strain (RVFWLS). CMR = cardiac magnetic resonance.

PRIMARY OUTCOME. Of the 544 patients in this study, 128 died during a median follow-up of 6.1 years (interquartile range: 3.4 to 9.8 years).

OUTCOMES AND RVFWLS. When stratified by the median value of RVFWLS (−16%), Kaplan-Meier analysis showed significantly increased risk of death in those with RVFWLS ≥median (log-rank $p < 0.001$) (**Central Illustration**). The continuous relationship between RVFWLS and the hazard of death is shown in the cubic spline in **Figure 2**. The univariable associations between RVFWLS and death are shown in Supplemental Table 1.

TABLE 1 Baseline Characteristics of the Study Population Stratified by RVFWLS Above and Below the Median (−16%)

		RVFWLS		
	Total	<Median (−16%)	≥Median (−16%)	p Value
Age, yrs	60.60 ± 18.6	59.14 ± 19.7	61.87 ± 17.2	0.123
Male	41.0	37.9	44.3	0.126
BMI, kg/m^2	27.3 ± 5.9	27.4 ± 6.0	27.1 ± 5.7	0.592
Diabetes	16.5	15.7	17.4	0.592
Hyperlipidemia	35.6	32.6	39.0	0.161
Hypertension	53.7	49.4	58.7	0.048
Smoking	27.3	26.9	27.8	0.830
Aspirin	42.4	39.5	45.7	0.191
Statin	29.8	27.6	32.3	0.284
ACE inhibitor	25.7	22.9	28.9	0.158
Beta-blocker	36.0	32.3	40.4	0.083
Pulmonary hypertension	14.3	12.5	16.3	0.208
Left-sided valve disease*	42.1	36.4	48.1	0.006
Heart rate, beats/min	79.8 ± 18.2	77.5 ± 15.8	82.4 ± 20.2	0.004
Systolic BP, mm Hg	122 ± 22	125 ± 23	120 ± 21	0.024
Diastolic BP, mm Hg	72 ± 14	72 ± 14	72 ± 14	0.950
LVEDV, ml	136 ± 65	126 ± 51	145 ± 75	<0.001
LVESV, ml	69 ± 60	55 ± 41	83 ± 72	<0.001
LVEF, %	52.4 ± 15.5	57.0 ± 12.0	47.4 ± 17.2	<0.001
LGE	36.6	25.4	48.5	<0.001
TAPSE, mm	14 ± 7	16 ± 7	11 ± 6	<0.001
Tricuspid valve annulus, mm	41 ± 8	40 ± 8	42 ± 8	0.017
RA area, cm^2	37 ± 14	36 ± 14	37 ± 14	0.284
RVEDV, ml	213 ± 99	200 ± 96	228 ± 101	0.001
RVESV, ml	137 ± 80	115 ± 65	159 ± 88	<0.001
RVEF, %	37.2 ± 14.2	42.1 ± 13.2	32.0 ± 13.5	<0.001

Values are mean ± SD or %. *Moderate or more left-sided valve disease.

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; LGE = late gadolinium enhancement; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RA = right atrial; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVFWLS = right ventricular free wall global longitudinal strain; TAPSE = tricuspid annular plane systolic excursion.

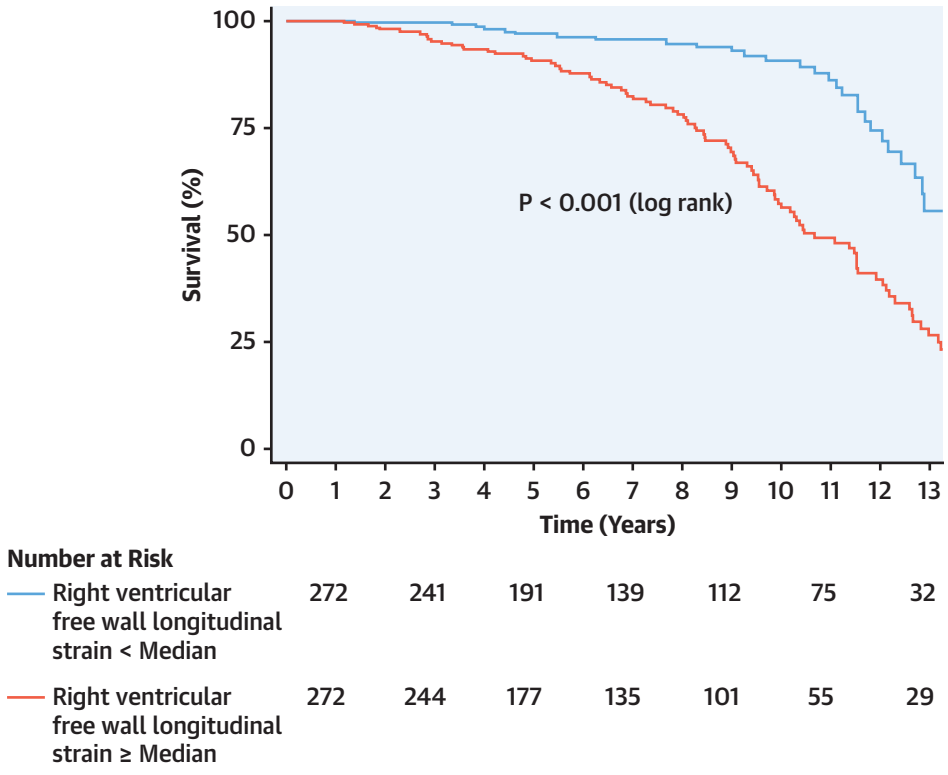
MULTIVARIABLE ANALYSIS AND INCREMENTAL PROGNOSTIC VALUE. After multivariable adjustment for clinical and imaging risk factors (age, sex, diabetes, hypertension, pulmonary hypertension, left-sided valve disease, LVEF, LGE, TAPSE, RVEDV, RVEF), RVFWLS remained a significant independent predictor of death (hazard ratio: 1.140; $p < 0.001$) (Table 2, Supplemental Table 2). In sequential nested Cox models, a model based on clinical variables alone (age, sex, diabetes, hypertension) was significantly improved by addition of imaging variables (pulmonary hypertension, left-sided valve disease, LVEF, LGE, TAPSE, RVEDV, RVEF), and further significantly improved by adding RVFWLS (Figure 3). Addition of RVFWLS into the model with clinical and imaging predictors resulted in a significant increase in the model chi-square value (from 31 to 78; $p < 0.001$).

DISCUSSION

This study shows that CMR feature-tracking-derived RVFWLS is an independent predictor of mortality in a multicenter population of patients with severe functional TR. We have demonstrated that RVFWLS provides prognostic information incremental to common clinical and CMR risk factors—including RV function and size, as well as LGE. These findings highlight the importance of long-axis RV function and suggest a role for feature-tracking RVFWLS in identifying patients at highest risk of death.

ROLE OF THE RV IN PROGNOSIS OF TR. Prognosis in significant TR is influenced by RV adaptation and remodeling (2,11). The volume overload caused by regurgitation leads to eventual RV dilation and dysfunction (2,6). In addition, RV dilation and dysfunction lead to worsening TR, resulting in a vicious cycle (2,6). However, this is a heterogenous process and has not been as well characterized and studied as for mitral regurgitation. Recently, Dietz et al. (11) evaluated the relative prognostic value of RV dilation versus RV dysfunction (assessed by TAPSE) in patients with moderate and severe functional TR using echocardiography. They found that

CENTRAL ILLUSTRATION **Kaplan-Meier Survival Curves in Patients With Severe Functional Tricuspid Regurgitation**



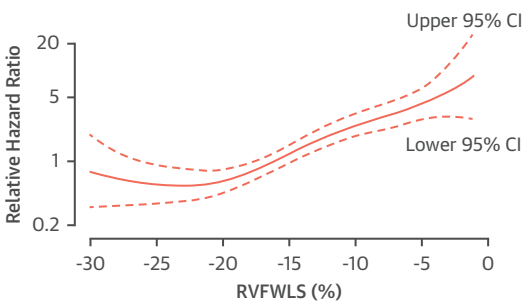
Romano, S. et al. J Am Coll Cardiol Img. 2021;14(8):1561–8.

Kaplan-Meier survival curves in patients with severe functional tricuspid regurgitation are stratified by right ventricular free wall longitudinal strain (RVFWLS) above and below the median value. Kaplan-Meier analysis showed significantly increased risk of death in those with RVFWLS ≥median (log-rank $p < 0.001$).

patients with the worst RV function (measured by TAPSE) had the worst survival regardless of the presence of RV dilation. Most prior studies have been limited by the ability of 2D echocardiography to adequately image the RV. In the current study, we used CMR as the gold standard technique for assessing RV volumes and EF.

Recently Prihadi et al. (26) examined the prognostic value of RVFWLS in 896 patients from a single center, with moderate or severe functional TR using speckle tracking echocardiography. They showed that RVFWLS was independently associated with all-cause death after adjustment to clinical and echocardiographic parameters. However, as stated by the investigators, their study was limited by use of 2D echo measures of RV size and function. We have now shown that feature-tracking RVFWLS provides independent and incremental prognostic information

FIGURE 2 **Relationship Between RVFWLS and Hazard of Death**



Hazard ratio (with 95% confidence intervals [CI]) are relative to those with median right ventricular free wall longitudinal strain (RVFWLS).

TABLE 2 Multivariable Model for Death

	Hazard Ratio (95% CI)	p Value
Age, per yr	1.024 (1.009–1.038)	0.001
Male	1.109 (0.751–1.637)	0.605
Diabetes	0.867 (0.555–1.353)	0.529
Hypertension	1.210 (0.782–1.872)	0.391
Pulmonary hypertension	1.392 (0.831–2.332)	0.208
Left-sided valve disease	0.912 (0.586–1.418)	0.683
LVEF, per %	1.015 (1.000–1.031)	0.052
LGE	1.052 (0.703–1.576)	0.804
TAPSE, per mm	1.020 (0.984–1.057)	0.275
RVEDV, per ml	1.001 (0.999–1.003)	0.580
RVEF, per %	1.008 (0.990–1.026)	0.405
RVFWLS, per %	1.140 (1.099–1.182)	<0.001

CI = confidence interval; other abbreviations as in Table 1.

even when using CMR with accurate measurements of RV volumes and functions as well as tissue assessment with LGE. These findings suggest that RVFWLS is a fundamental and early marker of RV dysfunction in severe TR.

RV CONTRACTION AND LONG-AXIS FUNCTION. The RV wall is predominantly composed of 2 layers. The superficial layer (approximately 25% of wall thickness) is formed primarily by circumferential fibers in a direction parallel to the atrioventricular groove that extend from one ventricle to another (27). The subendocardial RV layer is composed of longitudinally arranged fibers that pass through the apex toward the papillary muscles, tricuspid annulus, and RV outflow tract, and are continuous with those of the septum. Shortening of the longitudinal fibers draws the tricuspid valve toward the apex and is an important component of normal RV function (12).

Possibly because of their subendocardial location, the longitudinal fibers may be more sensitive to disturbance by various pathologies. At least in the LV, this appears to be related to greater compressive forces and higher oxygen consumption in the subendocardium (28,29).

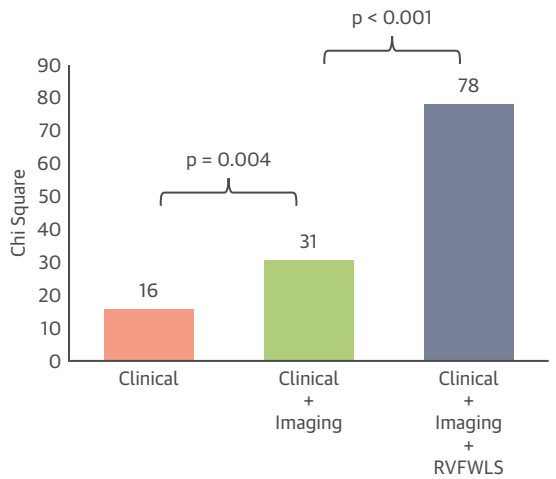
In this study, we have shown that reduction of RV long-axis function as detected by RVFWLS, is an independent predictor of mortality in patients with severe TR, possibly because it is an early marker of subclinical pathological processes affecting the subendocardial longitudinal fibers.

CLINICAL IMPLICATIONS. This study demonstrates the incremental prognostic value of feature-tracking-derived RVFWLS over clinical and CMR variables in patients with severe TR. It highlights the value of evaluating longitudinal RV free wall deformation to provide a more complete assessment of RV function than that provided by RV volumes and EF—even when these are assessed by the gold standard technique of CMR volumetric measurements.

To our knowledge, this is the first demonstration of the prognostic value of CMR in assessment of TR. Although echocardiography is the first-line modality for evaluation of TR, our findings suggest a potential role for evaluation of severe TR using CMR and feature-tracking RVFWLS. With the growing interest in transcatheter repair approaches for treatment of severe TR, early detection of RV dysfunction using feature-tracking RVFWLS may potentially play a role in determining optimal timing of intervention. How exactly this information will affect clinical care requires further investigation, and prospective studies are warranted to explore the role of feature-tracking RVFWLS in clinical decision-making. Ultimately, better identification of high-risk patients may allow closer follow-up and more directed therapies to be applied in a timely manner. Future studies will need to demonstrate that imaging-driven patient management improves specific outcomes before such approaches can be advocated.

STUDY LIMITATIONS. Although this is a multicenter study, the patients in this paper may not be representative of all patients with severe functional TR in the community. In this retrospective study, there

FIGURE 3 Sequential Nested Cox Models for Death



A model based on clinical variables alone (age, sex, diabetes, hypertension) was significantly improved by addition of imaging variables (pulmonary hypertension, left-sided valve disease, left ventricular ejection fraction, late gadolinium enhancement, tricuspid annular plane systolic excursion, right ventricular [RV] end-diastolic volume, RV ejection fraction), and further significantly improved by adding RV free wall longitudinal strain (RVFWLS).

is likely referral bias in undergoing the CMR exam, for example, resulting in exclusion of acutely sick patients, patients with large body size, severe renal impairment, or severe claustrophobia, or those with pacemakers and implantable cardioverter-defibrillators. At the time of scanning, there was no validated, widely used, single measure for classification of TR severity by CMR or echocardiography. TR regurgitant volume quantification was not included in the analysis because the necessary phase-contrast pulse sequences were not routinely performed at the time of clinical scanning in this retrospective study. Prospective studies using appropriate phase-contrast sequences to incorporate tricuspid regurgitant fraction should be performed in the future and would be of great interest.

Similar to echocardiography-derived strain, there are algorithmic differences between various CMR feature-tracking strain software programs, which may result in differing values (30). Thus, our findings would benefit from replication using other CMR feature-tracking strain vendors. Certain limitations of 2D feature tracking related to tracking through plane motion and limited temporal resolution should be borne in mind. RV vertical long-axis views were not used for RV strain assessment. This is because RV strain is typically measured in the 4-chamber view as recommended by expert consensus documents (31).

Information about downstream cardiovascular procedures, such as surgery or revascularization, was not available. However, this does not detract from the main findings of this study, that feature-tracking RVFWLS is a powerful predictor of death in these patients, independent of common clinical and imaging markers available at the time of CMR. Follow-up data were limited to the primary endpoint of all-cause death, and the cause of death was not known. However, many have argued that all-cause mortality is an extremely important and appropriate study endpoint because it is unbiased and clinically relevant, which is often not the case for other cardiac outcomes (32–34).

CONCLUSIONS

In this large multicenter study, CMR feature-tracking-derived RVFWLS is an independent predictor of mortality in patients with severe functional TR. We have demonstrated that RVFWLS provides prognostic information incremental to common clinical and CMR risk factors—including RV function and size, as well as LGE.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Weinsaft was supported by National Institutes of Health (NIH) grant R01 HL128278. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this multicenter study, feature-tracking RVFWLS measured during cine CMR is a significant independent predictor of mortality in patients with severe functional tricuspid regurgitation—incremental to common clinical and imaging risk factors.

TRANSLATIONAL OUTLOOK: How this information will affect clinical care requires further investigation, and future studies are warranted to explore the role of CMR-derived feature-tracking RVFWLS in clinical decision-making.

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KEY WORDS cardiac magnetic resonance, feature tracking, global longitudinal strain, mortality, prognosis, right ventricular function, tricuspid regurgitation

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