Prognostic Impact of Right Ventricular Strain in Isolated Severe Tricuspid Regurgitation

Rocio Hinojar, MD, PhD, Jose Luis Zamorano, MD, PhD, Ariana González Gómez, MD, Ana García-Martin, MD, PhD, Juan Manuel Monteagudo, MD, PhD, Inés García Lunar, MD, Angel Sanchez Recalde, MD, PhD, and Covadonga Fernández-Golfín, MD, PhD, *Madrid, Spain*

Background: Right ventricular (RV) systolic function is an established marker of outcomes in patients with severe tricuspid regurgitation (TR). Timely detection of RV dysfunction using conventional two-dimensional echocardiography is challenging. RV strain has emerged as an accurate and sensitive tool for the evaluation of RV function, with the capability to detect subclinical RV dysfunction. The aim of this study was to evaluate the prognostic value of RV strain parameters in early stages of severe TR.

Methods: Consecutive patients with at least severe TR (severe, massive, or torrential) and the absence of a formal indication for tricuspid valve intervention in secondary TR evaluated in the Heart Valve Clinic were prospectively included. RV systolic function was measured using conventional echocardiographic indices (RV fractional area change, tricuspid annular plane systolic excursion, and Doppler tissue imaging S wave [S′]) and speckle-tracking echocardiography–derived automatic peak global longitudinal strain and free wall longitudinal strain (FWLS) using an automated two-dimensional strain analytic software. A combined end point of hospital admission due to heart failure or all-cause mortality was defined.

Results: A total of 266 patients were enrolled in the study, and 151 were ultimately included. Strain parameters detected a higher percentage of abnormal RV values compared with conventional indices. During a median follow-up period of 26 months (interquartile range, 13-42 months), 35% of the patients reached the combined end point. Cumulative event-free survival was significantly worse in patients with impaired RV global longitudinal strain and RV FWLS. Conventional indices of RV systolic function were not associated with outcomes ($P > .05$ for all). On multivariate analysis, RV FWLS was independently associated with mortality and heart failure (adjusted hazard ratio for abnormal RV FWLS, 5.90; 95% CI, 3.17-10.99; $P < .001$).

Conclusion: In early stages of severe TR, RV FWLS is more frequently impaired compared with conventional indices of RV function. Among all parameters, RV FWLS is the strongest predictor of mortality and heart failure, independent of additional prognostic markers. (J Am Soc Echocardiogr 2023;36:615-23.)

Keywords: Tricuspid regurgitation, RV function, Strain

The management of patients with severe isolated tricuspid regurgitation (TR) remains challenging despite increasing evidence of its independent effect on survival.[1-7] Although medical therapy and cardiac surgery have not yet demonstrated a beneficial effect on long-term prognosis,[6-9] recent transcatheter tricuspid valve therapies have been associated with greater survival and reduced heart failure hospitalizations.[10] The optimal timing for tricuspid intervention is crucial to improve results. Precise evaluation of right ventricular (RV) performance is one the most important challenges for selecting patients who may benefit from valve intervention.

In primary TR, RV dilatation or dysfunction represents the current formal indication for valve intervention in the absence of significant symptoms, whereas in secondary TR, the benefit of surgical correction is not well established.[6,7] European Society of Cardiology

From the Cardiology Department, University Hospital Ramón y Cajal, Madrid, Spain (R.H., J.L.Z., A.G.G., A.G.-M., J.M.M., I.G.L., A.S.R., C.F.-G.); Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain (R.H., J.L.Z., A.G.G., J.M.M., A.S.R., C.F.-G.); CIBERCV, Instituto de Salud Carlos III, Madrid, Spain (J.L.Z., I.G.L., C.F.-G.); and Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain (I.G.L.).

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Reprint requests: Rocio Hinojar, MD, PhD, University Hospital Ramón y Cajal, Carretera de Colmenar Km 9.100, 28034 Madrid, Spain (E-mail: *rociohinojar@gmail.com*).

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Abbreviations

AUC = Area under the curve
BNP = Brain natriuretic peptide
CoV = Coefficient of variation
FAC = Fractional area change
FWLS = Free wall longitudinal strain
GLS = Global longitudinal strain
HR = Hazard ratio
IVC = Inferior vena cava
LV = Left ventricular
NYHA = New York Heart Association
RA = Right atrial
RAP = Right atrial pressure
RV = Right ventricular
STE = Speckle-tracking echocardiography
TAPSE = Tricuspid annular plane systolic excursion
TR = Tricuspid regurgitation
VC = Vena contracta

guidelines (but not American College of Cardiology/American Heart Association guidelines) include RV dilatation as a potential indication for surgery in the absence of severe systolic dysfunction or severe pulmonary hypertension. However, the evaluation of RV function is particularly difficult. RV dimension and function are commonly evaluated using two-dimensional transthoracic echocardiography. Transthoracic echocardiographic evaluation is made challenging by the complex RV geometry (crescentic and highly trabeculated) and position (retrosternal and anterior to the left ventricle). An integrative approach of different RV parameters is endorsed in the guidelines to assess RV systolic function,[11,12] given the insufficient accuracy of each measure when interpreted separately. However, even this approach has low reproducibility among operators given the wide range for subjective interpretation. In addition, these parameters are influenced by changes of preload conditions and can remain unaffected until late stages of the disease. At the current moment, defined cutoff values for RV dilation or dysfunction to support intervention are lacking.

Speckle-tracking echocardiography (STE) allows the assessment of systolic function by evaluating active shortening of the myocardium. STE does not rely on geometric assumptions, is not dependent on the imaging angle, and is less affected by preload conditions than indices of ejection fraction. In left ventricular (LV) cardiomyopathies, STE has shown to be more sensitive than LV ejection fraction to detect LV dysfunction, with excellent reproducibility and incremental ability to predict impaired prognostic outcomes.[13] However, the role of STE in RV evaluation has been less extensively studied. RV strain has been proposed for RV evaluation in pulmonary embolism, pulmonary hypertension, and heart failure and has been shown to be feasible and reproducible.[14-16] Recently, European Society of Cardiology guidelines include RV strain evaluation in severe TR to overcome the limitations of conventional RV function indices.[6] However, for the moment, there is scarce information endorsing the role of RV speckle-tracking echocardiographic parameters in severe TR. The aim of this study was to evaluate the additional prognostic value of RV speckle-tracking echocardiographic parameters in the management of consecutive patients with isolated, at least severe TR.

METHODS

Study Design and Patients

Consecutive patients with at least severe TR evaluated in the Heart Valve Clinic were prospectively included in this observational study from 2016 to 2019. Exclusion criteria for all subjects included previous episodes of heart failure or a formal indication for tricuspid valve intervention in secondary TR, the presence of significant (greater than mild) uncorrected left heart valve disease or alternative causes of RV remodeling (previous RV infarction, arrhythmogenic RV cardiomyopathy, congenital heart disease, or TR secondary to precapillary pulmonary hypertension in the context of lung disease and/or hypoxia).

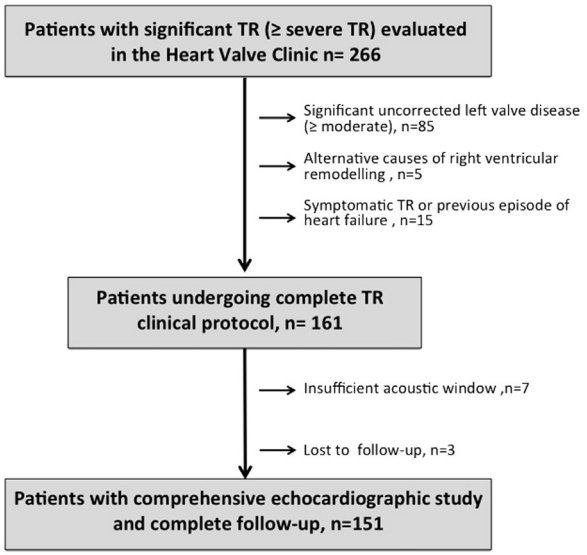

Figure 1 Patient flowchart.

Figure 1 shows the flowchart for patient selection. At our center, patients with at least severe TR evaluated in the Heart Valve Clinic undergo clinical evaluation, serum biomarker evaluation, and comprehensive echocardiography at their first visits and every 6 months per clinical protocol while they remain clinically stable (follow-up may change if clinical status deteriorates).

Clinical characteristics were recorded for all patients, including age, gender, body mass index, and the presence of traditional cardiovascular risk factors. Baseline functional status was determined using the New York Heart Association (NYHA) functional classification. Biochemical analysis, including renal function, hemogram, brain natriuretic peptide (BNP) level, and liver function enzymes, was performed in all patients.

The study protocol was reviewed and approved by the local institutional ethics committees. Written informed consent to perform the protocol was obtained from all patients. All procedures were carried out in accordance with the Declaration of Helsinki (2000).

Echocardiography

The first transthoracic echocardiographic study after the first medical visit in the Heart Valve Clinic was used for analysis. Comprehensive transthoracic echocardiographic examinations were performed using a commercially available ultrasound system (EPIQ; Philips Medical Systems). Parasternal, apical (four, two, and three chamber), and subcostal views were used to acquire two-dimensional, color, pulsed-wave, and continuous-wave Doppler data according to current recommendations. RV-focused views from the apical approach were also acquired in all patients.[10]

LV ejection fraction was quantified using the Simpson biplane method and expressed as a percentage. Concomitant left-sided

HIGHLIGHTS

- RV FWLS is a sensitive marker of RV dysfunction.
- RV FWLS is more often impaired compared with conventional indices.
- In early stages of severe TR, RV FWLS has a stronger association with outcomes.
- RV FWLS predicts outcomes independently of additional prognostic markers.
- RV FWLS should be considered in diagnostic algorithms for severe TR.

valvular heart disease and LV diastolic dysfunction were assessed according to the current recommendations.[11,17]

The severity of TR was evaluated according to current guidelines combining different semiquantitative and quantitative parameters.[18,19] At least severe TR was defined as a TR jet of at least severe grade according to the new grading scheme (severe, massive, or torrential TR; effective regurgitant orifice area ≥ 40 mm^2, regurgitant volume ≥ 45 mL, vena contracta [VC] [biplane] ≥ 7 mm).[18]

TR etiology was divided into four main categories as recently proposed: primary or organic TR, secondary atrial TR, secondary ventricular TR, and cardiac implantable electronic device–related TR.[20]

RV assessment was performed in the RV-focused four-chamber view (Figure 2). RV end-diastolic and end-systolic areas were traced, and RV fractional area change (FAC) was calculated using the following formula: FAC = [(diastolic area − systolic area)/diastolic area] × 100. Tricuspid annular plane systolic excursion (TAPSE) was calculated on M-mode recordings of the lateral tricuspid annulus. RV S′ or systolic excursion velocity by Doppler tissue imaging was measured placing the pulse Doppler sample in the lateral tricuspid annulus and reading the highest systolic velocity. Abnormality of each parameter was defined on the basis of recommended thresholds.[11,21]

Two-dimensional RV strain analysis was performed using novel, fully automated two-dimensional strain analytic software (AutoStrain; Philips Medical Systems) from RV-focused apical views. The software automatically determined the RV endocardial border using a knowledge-based artificial intelligence algorithm and performed speckle-tracking analysis through one complete cardiac cycle, generating regional strain curves and both RV global longitudinal strain (GLS) and free wall longitudinal strain (FWLS). The accuracy of RV boundary contour registration was visually assessed in each patient, and editing was possible when necessary. Abnormal RV FWLS was defined as RV FWLS $> -20\%$, as recommended.[11,21] Abnormal RV GLS was not defined, given the lack of recommended normal reported values.

Right atrial (RA) area was measured in RV-focused four-chamber apical views. RA volume was measured using the biplane area-length method.

Systolic pulmonary artery systolic pressure was estimated on the basis of the peak TR velocity and the TR velocity–derived TR pressure gradient, taking into account noninvasive estimates of RA pressure (RAP). Examination of the inferior vena cava (IVC) was performed in the subcostal view with the patient in a supine position. IVC diameter was measured 1.0 to 2.0 cm from the junction with the right atrium perpendicular to the IVC long axis. Collapsibility was assessed

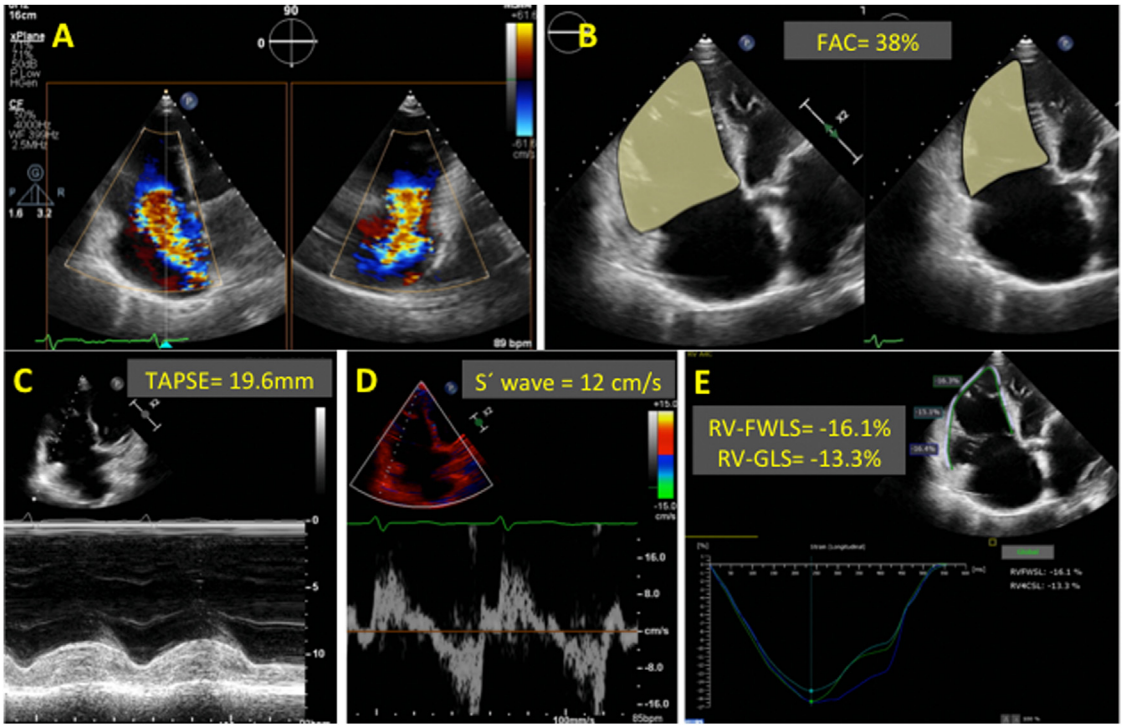

Figure 2 Representative examples of different measures of RV systolic function in patients with severe TR. **(A)** X plane with color Doppler. **(B)** RV FAC is calculated as the ratio of RV end-diastolic area and RV end-systolic area. **(C)** TAPSE by M mode imaging. **(D)** S-wave (S′) velocity by Doppler tissue imaging. **(E)** RV FWLS and RV GLS by STE.

as percentage decrease in diameter during the sniff test. An IVC diameter of <2.1 cm that collapsed >50% with a sniff was assigned an RAP of 3 mm Hg, IVC ≥ 2.1 cm that collapsed <50% was assigned an RAP of 15 mm Hg, IVC diameter < 2.1 cm that collapsed <50% or IVC diameter ≥ 2.1 cm that collapsed >50% was assigned an intermediate RAP of 8 mm Hg.[11]

The interobserver variability of RV strain was assessed in 25 randomly chosen patients. All measures were performed by cardiologists with expertise in cardiac imaging, who were blinded to patient outcomes.

Clinical Outcomes

Clinical data were obtained prospectively from hospital records in the Heart Valve Clinic and from direct communication with patients. A combined end point of hospital admission for heart failure and all-cause mortality at follow-up was defined.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS) and Stata version 14.1 (StataCorp). Normality of distributions was tested using the Kolmogorov-Smirnov statistic. Categorical data are expressed as percentages and continuous variables as mean ± SD or median (interquartile range), as appropriate. For comparison of two normally distributed variables, Student's *t* test for continuous variables and the χ^2 test for categorical variables were used, as appropriate. Multivariable Cox analysis was performed with forward selection (likelihood ratio) modeling to determine independent associations with outcome (adjusted hazard ratio [HR] and 95% CI), accounting for the rule of thumb for logistic and Cox models with a minimum of 10 outcome events per predictor variable. We limited our selection on the basis of the biological plausibility of each variable, its relevance on current clinical decision-making, and the association with outcomes on univariate analyses. Multicollinearity was avoided using the strongest variable associated with outcomes in time-dependent receiver operating characteristic curves and confirmed by a low variance inflation factor (<2). Areas under the curves (AUCs) were calculated and compared. Event distributions according to RV strain parameters were calculated according to the Kaplan-Meier method and compared by means of the log-rank test. Interobserver agreement for RV strain values was measured using the intraclass correlation coefficient (*r*) and coefficient of variation (CoV).

All tests were two-tailed, and a *P* value of <.05 was considered to indicate statistical significance.

RESULTS

A total of 266 patients were evaluated in the Heart Valve Clinic for at least severe TR. After exclusion of those patients who fulfilled exclusion criteria or those with incomplete clinical or imaging data, 151 patients were included in this study (Figure 1). Demographic data and baseline characteristics of patients are presented in Table 1. Most of the patients were women, and the mean age was 78 ± 7 years. Ninety-one percent were in NYHA functional class I or II. Regarding etiology, 4% of the patients had primary TR, 8% had cardiac implantable electronic device–related TR, 40% had atrial functional TR, and 48% had functional ventricular TR.

Echocardiographic parameters are shown in Table 2. The majority of the patients (83%) showed severe TR, 13% had massive TR, and 4% had torrential TR. Mean values of the different parameters of RV function are described in Table 2. Fully automatic RV strain was performed in 90% of the cases, but manual editing was necessary in 15 (10%).

RV FWLS identified a higher percentage of abnormal values (Figure 3) compared with conventional parameters. In the subgroup of patients with normal values of TAPSE, normal S′ waves, and normal FAC ($n = 112$), RV FWLS was impaired in 39% of the patients.

Patients with massive and torrential TR showed worse RV FWLS and RV GLS compared with severe TR (RV FWLS, massive TR plus torrential TR vs severe TR: −17.3 ± 5% vs −21.8 ± 5%, $P = .007$; RV GLS, massive TR plus torrential TR vs severe TR: −15.8 ± 5% vs −18.7 ± 5%, $P = .05$).

Interobserver agreement for RV strain values across the whole cohort was high (for RV GLS, $r = 0.96$ and CoV = 3.9; for RV FWLS, $r = 0.97$ and CoV = 4.4).

Follow-Up and Outcomes

During a median follow-up period of 26 months (interquartile range, 13-42 months), 53 patients (35%) reached the combined end point. Fifty-two patients (34%) were admitted for HF, and one (0.6%) died as the first event. Of the patients admitted for HF, 10 died during follow-up. Twenty-six patients underwent tricuspid valve surgery (seven tricuspid annuloplasty and 19 tricuspid valve prosthesis), and 11 underwent percutaneous tricuspid annuloplasty with the Cardioband device (Edwards Lifesciences).

Tables 1 and 2 show differences in clinical, biomarker, and echocardiographic parameters between patients with and those without events. Patients with events showed lower values of hemoglobin, higher basal BNP levels, and higher cholestatic liver enzymes (serum alkaline phosphatase and gamma-glutamyl transpeptidase). Regarding imaging parameters, patients with events showed more severe TR, higher RV diameters, higher RV end-diastolic and end-systolic areas, higher RA volumes, and worse values of RV strain (including RV GLS and RV FWLS; $P < .05$ for all). TAPSE, S′ wave, and FAC were not different between patients with and those without events ($P > .05$ for all).

Univariate Cox regression analysis demonstrated that female gender, higher NYHA functional class, and higher levels of hemoglobin, BNP, alkaline phosphatase, and gamma-glutamyl transpeptidase were significantly associated with all-cause mortality and heart failure (Table 3). Regarding imaging parameters, all severity measurements of TR (effective regurgitant orifice, VC, and regurgitant volume) were predictive of events ($P < .05$ for all). Different parameters of RV size (basal and mid end-diastolic diameters and RV end-diastolic and end-systolic areas) were also significantly associated with outcomes. Regarding parameters of RV function, only RV GLS and RV FWLS were significantly associated with outcomes. TAPSE, S′ wave, and FAC had no significant relationships with events. RV FWLS was associated with events even in the subgroup of patients with massive and torrential TR (HR per 1% of RV FWLS, 1.11; 95% CI, 1.03-1.19; $P = .006$).

Receiver operating characteristic curves were used to include the strongest variables for each predictor in the multivariable analysis. Regarding serum biomarkers, BNP remained the parameter more strongly associated with outcomes (AUC, BNP vs gamma-glutamyl transpeptidase vs alkaline phosphatase: 0.70 vs 0.65 vs 0.61;

Table 1 Demographic and clinical characteristics in all patients and comparisons between patients with and those without events

Variable	All patients (*n* = 151)	Patients with events (*n* = 53)	Patients without events (*n* = 98)	*P*
Age, y	78 ± 7	78 ± 8	77 ± 8	.80
Gender, female	104 (69)	30 (57)	74 (75)	.02
Type 2 diabetes mellitus	26 (17)	12 (23)	14 (14)	.20
Hypertension	88 (58)	31 (58)	57 (58)	.81
Hypercholesterolemia	66 (44)	23 (43)	43 (44)	.84
Smoking	15 (10)	8 (15)	7 (7)	.16
Atrial fibrillation	133 (88)	49 (92)	84 (86)	.30
Coronary artery disease	12 (8)	5 (9)	7 (7)	.53
Previous cardiac surgery	66 (44)	24 (45)	42 (43)	.84
TR etiology				.27
Primary TR	6 (4)	2 (4)	4 (4)	
Functional TR				
Atrial TR	60 (40)	20 (37)	40 (41)	
Ventricular TR	73 (48)	28 (52)	45 (46)	
CIED related TR	12 (8)	3 (6)	9 (9)	
NYHA functional class				.002
I/II	138 (91)	45 (85)	93 (95)	
III	13 (9)	8 (15)	5 (5)	
IV	0 (0)	0 (0)	0 (0)	
Diuretic treatment				
Loop diuretics	35 (23)	18 (34)	17 (17)	
Thiazide diuretics	2 (1)	2 (0.4)	0 (0)	
Potassium-sparing diuretics	27 (18)	10 (19)	17 (17)	
Biochemistry				
Creatinine, mg/dL	0.9 ± 0.22	1.03 ± 0.33	0.97 ± 0.8	.50
Hemoglobin, g/dL	13.9 ± 2	12 ± 1.8	13.2 ± 1.6	<.001
BNP, pg/mL	140 (82-234)	180 (115-321)	107 (74-167)	<.001
Total bilirubin, mmol/L	0.8 (0.6-1.2)	0.82 (0.6-1.2)	0.76 (0.6-1.2)	.78
ASAT, U/L	21 (18-25)	21 (16-21)	21 (18-25)	.35
ALAT, U/L	15 (12-15)	15 (12-19)	16 (13-20)	.18
GGT, U/L	50 (27-90)	71 (27-118)	43 (27-66)	.013
LDH, U/L	228 (190-278)	231 (198-277)	225 (187-278)	.69
ALP, U/L	80 (67-98)	84 (67-130)	77 (67-91)	.045

ALAT, Alanine aminotransferase; *ALP*, alkaline phosphatase; *ASAT*, aspartate aminotransferase; *CIED*, cardiovascular implantable electronic device; *GGT*, gamma-glutamyl transpeptidase; *LDH*, lactate dehydrogenase.
Data are expressed as mean ± SD, number (percentage), or median (IQR).

$P > .05$). Biplane VC was better than effective regurgitant orifice and regurgitant volume to predict outcomes (AUC, 0.70 vs 0.65 vs 0.61, respectively; $P < .01$). According to RV size (AUC, RV end-diastolic area vs RV-end-systolic area vs RV basal vs RV mid diameter: 0.73 vs 0.70 vs 0.63 vs 0.62; $P < .05$), RV end-diastolic area yielded the strongest value associated with outcomes. RV FWLS was shown to be superior to RV GLS to predict events (0.94 vs 0.82, respectively; $P < .05$ for all).

In a multivariable analysis (in a model including NYHA functional class, BNP level, biplane VC, RV end-diastolic area, and RV FWLS), RV FWLS, biplane VC, and basal NYHA functional class remained independent predictors of HF and mortality (Table 3; likelihood ratio $\chi^2 = 40.2$, $P < .001$). Abnormal RV FWLS was associated with a 5.90-fold increased risk for HF or death (adjusted HR, 5.90; 95% CI, 3.17-10.99; $P < 0.001$; Figure 4).

Cutoff Values of Strain on the Basis of Outcome

On receiver operating characteristic curve analysis, a cutoff value for RV FWLS of ≥−21.5% yielded the best accuracy to predict outcomes (AUC, 0.82; 95% CI, 0.74-0.89; $P < .001$; sensitivity, 80%; specificity, 74%). For RV GLS, a cutoff value of ≥−18.5% was defined (AUC, 0.80; 95% CI, 0.72-0.88; $P < .001$; sensitivity, 76%; specificity, 71%).

Table 2 Echocardiographic parameters

Variable	All patients (*n* = 151)	Patients with events (*n* = 53)	Patients without events (*n* = 98)	*P*
Left chambers				
LV EDV index, mL/m^2	47 ± 24	46 ± 18	44 ± 17	.29
LV ESV index, mL/m^2	17 ± 9	17 ± 9	15 ± 6	.12
LV SV, mL/m^2	27 ± 9	26 ± 9	28 ± 10	.41
LV ejection fraction, %	64 ± 9	62 ± 10	65 ± 8	.20
LA volume, mL/m^2	54 (37-78)	70 (37-90)	53 (36-72)	.24
Average E/e′ ratio	11 ± 4	10 ± 4	11 ± 4	.40
Right chambers				
RV basal diameter, mm	44 ± 0.7	47 ± 0.6	42 ± 0.6	.007
RV mid diameter, mm	34 ± 0.8	38 ± 0.9	31 ± 0.6	.007
sPAP, mm Hg	40 ± 12	45 ± 14	41 ± 12	.47
Peak TR velocity, m/sec	2.73 ± 0.5	2.68 ± 0.6	2.76 ± 0.5	.34
RA maximum area, cm^2	29 ± 8	30.7 ± 7	28.6 ± 13	.23
RA maximum volume, mL	107 (77-152)	122 (90-163)	90 (65-133)	.02
RV end-diastolic area, cm^2	22 ± 6	25.4 ± 6	19.9 ± 6	<.001
RV end-systolic area, cm^2	12 ± 4	13.7 ± 4	11.3 ± 4	.002
RV FAC, %	43.5 ± 13	42 ± 17	45 ± 8	.10
TAPSE, mm	20.6 ± 4	20.3 ± 4	20.7 ± 4	.59
DTI S′ wave, cm/sec	10.3 ± 2	10.15 ± 2	10.4 ± 2	.46
RV free wall strain, %	−22.0 ± 6	−17.0 ± 5	−23.9 ± 4	<.001
RV GLS, %	−18.3 ± 5	−14.9 ± 5	−20.3 ± 4	<.001
TR				
Tricuspid annulus, mm	42 ± 0.7	42 ± 0.6	40 ± 0.7	.84
TR biplane VC, mm	9.1 ± 0.3	10.2 ± 0.4	7.8 ± 0.3	.03
ERO, cm^2	0.44 (0.34-0.60)	0.54 (0.37-0.73)	0.40 (0.34-0.52)	.003
TR regurgitant volume, mL	36 (29-46)	42 (32-55)	35 (28-43)	.013

DTI, Doppler tissue imaging; *EDV*, end-diastolic volume; *ERO*, effective regurgitant orifice; *ESV*, end-systolic volume; *LA*, left atrial; *sPAP*, systolic pulmonary artery pressure; *SV*, stroke volume.
Data are expressed as mean ± SD or median (interquartile range).

In the subgroup of patients with normal RV systolic function on the basis of conventional indices (normal TAPSE, normal Doppler tissue imaging S′, and normal FAC), the proposed RV FWLS cutoff value remained an independent predictor of events (HR, 3.5; 95% CI, 1.6-6.99; $P = .001$).

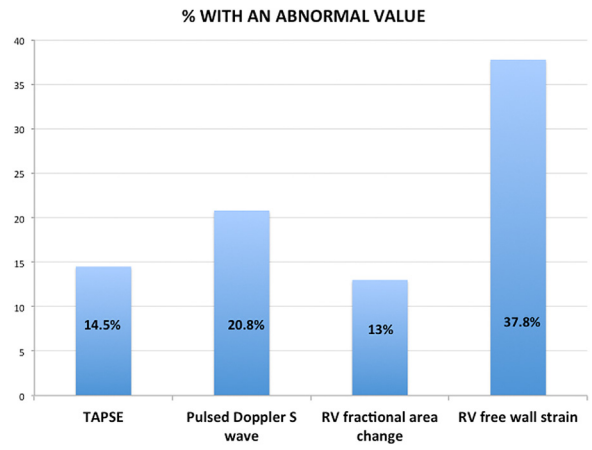

Figure 3 Distribution of abnormal values of RV function on the basis of the defined thresholds (RV FAC < 35%, TAPSE < 17 mm, and RV FWLS > −21%).

DISCUSSION

Our results demonstrate that RV strain parameters are able to identify early RV involvement in patients with at least severe TR and are associated with mortality and heart failure. RV systolic function is determinant in the prognosis of patients with severe TR. In early stages of tricuspid valve disease, before the development of heart failure, conventional echocardiographic indices of RV systolic function remain within normal ranges and fail to demonstrate associations with clinical outcomes.

Previous experimental studies in different conditions of RV volume overload have also demonstrated that RV functional reserve and myocardial contractility are impaired, although conventional indices of RV function remain preserved for long periods of time.[22-24] Our results confirm that RV FWLS is more frequently impaired and has a stronger association with outcomes compared with conventional indices. RV FWLS is impaired in a significant proportion of patients with normal TAPSE, S′ waves, and FAC. Moreover, advanced parameters of RV function (both RV FWLS and RV GLS) significantly affect clinical prognosis. We show that the combination

Table 3 Results of univariate and multivariate analyses in prediction of the outcome end points

	Univariate		Multivariate (LR χ^2 = 40.2)	
	Unadjusted HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.01 (0.99-1.03)	.29		
Gender, female	2.07 (1.19-3.60)	.01	—	—
NYHA functional class	2.20 (1.39-3.51)	.001	1.92 (1.22-3.05)	.005
Hemoglobin,	0.78 (0.68-0.89)	<.001	—	—
BNP	1.01 (1.01-1.01)	<.001	1.00 (1.00-1.01)	.09
GGT	1.01 (1.00-1.01)	<.001	—	—
ALP	1.01 (1.01-1.02)	<.001	—	—
LVEF	0.98 (0.95-1.01)	.18	—	—
LV ESV index	1.03 (1.01-1.06)	.02	—	—
RV basal diameter	1.93 (1.12-3.34)	.02	—	—
RV mid diameter	2.17 (1.28-3.69)	.004	—	—
RA maximum volume	1.00 (0.99-1.01)	.23	—	—
sPAP	1.01 (0.99-1.03)	.45		
RV end-diastolic area	1.09 (1.05-1.14)	<.001	1.08 (0.96-1.05)	.74
RV end-systolic area	1.12 (1.06-1.20)	<.001	—	—
RV FAC	12.7 (0.47-342.2)	.13	—	—
TAPSE	0.98 (0.91-1.04)	.49	—	—
DTI S′ wave	0.95 (0.82-1.12)	.55	—	—
RV GLS,%	1.16 (1.10-1.22)	<.001	—	—
RV free wall strain	1.15 (1.10-1.21)	<.001	1.14 (1.08-1.20)	<.001
Biplane VC	1.96 (1.40-2.77)	<.001	2.24 (1.45-3.47)	<.001
ERO	1.66 (1.15-2.39)	.006	—	—
TR regurgitant volume	1.01 (1.00-1.01)	.03	—	—

ALP, Alkaline phosphatase; *DTI*, Doppler tissue imaging; *ERO*, effective regurgitant orifice; *ESV*, end-systolic volume; *GGT*, gamma-glutamyl transpeptidase; *LR*, likelihood ratio; *LVEF*, LV ejection fraction; *sPAP*, systolic pulmonary artery pressure.
For univariate analyses, results are presented as unadjusted HRs with 95% CIs. Multivariate analyses were performed with a forward selection (LR) of variables and the adjusted HR (95% CI) accounting for the rule of thumb for logistic Cox models with a minimum of 10 outcome events per predictor variable. To set up the interdependency of measures, we avoided multicollinearity using "the strongest of the group" approach.

of basal functional status, TR severity, and RV systolic function (specifically measured by RV FWLS) independently predicts mortality and heart failure events.

TR management is currently challenging, and the optimal timing for intervention remains controversial. Untreated severe TR is associated with poor outcomes; mortality in surgical series remains significantly high, up to 24% during the first year of follow-up.[25] For the time being, surgery has failed to demonstrate improved long-term survival compared with medical management,[8] and delayed timing of intervention may explain the lack of survival benefit.

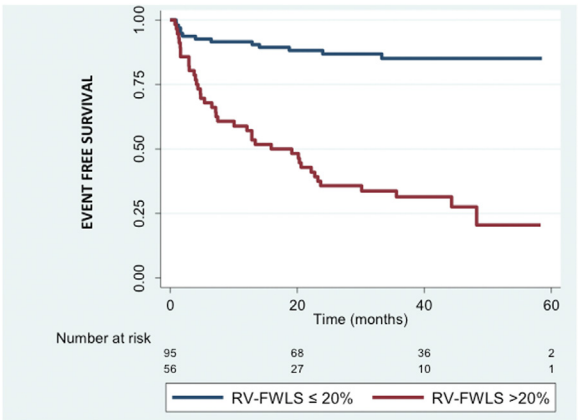

Figure 4 Kaplan-Meier survival curves according to RV FWLS. Patients with abnormal RV FWLS (>−21%) showed a significantly higher rate of heart failure events and cardiovascular death.

RV performance is crucial in the evaluation of patients with TR. Transthoracic echocardiography is the most available imaging technique, but conventional RV function indices fail to detect RV dysfunction on time. In stable patients without previous episodes of heart failure, these indices remain within normal ranges for most patients, and subtle RV dysfunction, if present, is not detected.

Speckle-tracking echocardiographic parameters are more sensitive and accurate for the diagnosis of RV systolic dysfunction in patients with pulmonary hypertension, heart failure, and different cardiomyopathies. Our results confirm that speckle-tracking echocardiographic parameters are also more sensitive in severe TR, on the basis of the significant proportion of patients with abnormal RV FWLS but normal conventional indices. In the last 2 years, the role of RV strain in TR has been evaluated in some studies,[26-29] but none has been prospectively designed in patients with isolated at least severe TR without previous episodes of heart failure and absence of concomitant uncorrected heart valve disease. These studies also demonstrated the limitations of the most commonly used echocardiographic indices to assess RV function in patients with TR. They also showed the superior

prognostic value of RV FWLS compared with TAPSE and FAC. Despite the unquestionable value of their findings, the population differs significantly from the population in our study. In the study of Prihadi *et al.*,[26] patients were selected on the basis of previously obtained echocardiograms irrespective of symptomatic status and data were retrospectively analyzed. Moderate TR was present in 79.9% of patients, and only 20.1% had severe TR. Concomitant left valve disease was frequent: 52.7% had at least moderate mitral regurgitation or aortic stenosis. Similarly, Bannehr *et al.*[28] retrospectively studied patients undergoing transthoracic echocardiography, irrespective of the indication and clinical status. Only 5.3% showed severe TR, and concomitant severe left valve disease was frequent. Ancona *et al.*[27] studied patients with symptomatic severe TR (91.2% with right heart failure) with a high prevalence of at least moderate concomitant mitral valve disease. Recently, Akintoye *et al.*[29] demonstrated the value of RV FWLS in a retrospectively selected cohort of asymptomatic patients with at least moderate TR. The TR cohort was different from ours: a low percentage of atrial functional TR, as patients with sustained atrial fibrillation were excluded; low ventricular functional TR because of previous corrected valve disease, as the investigators included only 5% with left valve surgery; and no cardiac implantable electronic device–related TR.

We show for the first time the prognostic value of RV strain parameters in a homogeneous population of stable patients under follow-up for isolated significant TR. In this scenario of an early stage, conventional indices of RV function remain within normal ranges and fail to stratify patient risk. However, patients with predefined abnormal RV FWLS showed a 5.90-fold increased risk for heart failure or death. In our cohort of patients, RV FWLS $\geq -21.5\%$ and RV GLS $\geq -18.5\%$ had the best accuracy to predict cardiovascular outcomes. These cutoff values correspond fairly well to the recommended thresholds for abnormality of strain parameters[11,21] and are in line with the described thresholds in previous studies.[26-30]

Our results offer additional insights into the clinical relevance of the early detection of RV dysfunction and may help overcome an important gap in clinical management. FWLS may be positioned as an earlier and more robust parameter of RV dysfunction in isolated severe TR. Proposed strain thresholds provide a step forward for future prospective studies or clinical trials to establish definitive optimal timing for intervention in severe TR.

Recently, a dedicated risk score model (TRI-SCORE) for the preoperative assessment of isolated tricuspid valve surgery was proposed, including for the first time the impact of RV function on outcomes.[31] Despite its value to support clinical decision-making, the authors defined moderate or severe RV dysfunction on the basis of conventional parameters (TAPSE, Doppler tissue imaging S′, and visual assessment), acknowledging the intrinsic limitations of these parameters in the setting of severe TR. Strain may replace conventional parameters in the near future to define and stratify RV dysfunction, as novel percutaneous strategies have emerged and potentially offer an opportunity to reduce TR at lower procedural risk.

Several limitations of the present study must be acknowledged. This was an observational, single-center study with a relatively small sample size, which may limit the overall power of the study. Abnormal values of RV GLS were not predefined, given the lack of established normative references. RV ejection fraction from three-dimensional echocardiography or cardiovascular magnetic resonance imaging was not available to provide direct comparison of RV systolic function as measured on STE.

CONCLUSION

Clinical outcomes demonstrate that RV strain parameters are superior to conventional indices of RV function in stable patients with at least severe TR. In early clinical stages, conventional indices of RV function remain preserved and fail to stratify patient risk. Among all parameters of RV function, RV FWLS is the strongest independent predictor of HF and mortality.

REFERENCES

1. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the framingham heart study). Am J Cardiol 1999;83:897-902.
2. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. JACC Cardiovasc Imaging 2019;12:433-42.
3. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43:405-9.
4. Santoro C, Marco Del Castillo A, González-Gómez A, et al. Mid-term outcome of severe tricuspid regurgitation: are there any differences according to mechanism and severity? Eur Heart J Cardiovasc Imaging 2019;20:1035-42.
5. Vieitez JM, Monteagudo JM, Mahia P, et al. New insights of tricuspid regurgitation: a large-scale prospective cohort study. Eur Heart J Cardiovasc Imaging 2021;22:196-202.
6. Vahanian A, Beyersdorf F, Praz F, et al., ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;ehab395.
7. Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American heart association Joint Committee on clinical Practice guidelines. J Thorac Cardiovasc Surg 2021;162:e183-353.
8. Axtell AL, Bhambhani V, Moonsamy P, et al. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. J Am Coll Cardiol 2019;74:715-25.
9. Vassileva CM, Shabosky J, Boley T, et al. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. J Thorac Cardiovasc Surg 2012;143:1043-9.
10. Taramasso M, Benfari G, van der Bijl P, et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. J Am Coll Cardiol 2019;74:2998-3008.
11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
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;30:303-71.
13. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 2014;100:1673-80.
14. Longobardo L, Suma V, Jain R, et al. Role of two-dimensional speckle-tracking echocardiography strain in the assessment of right ventricular systolic function and comparison with conventional parameters. J Am Soc Echocardiogr 2017;30:937-46.e6.

15. Li Y, Sun C, Zhang L, et al. Feasibility, reproducibility, and prognostic value of fully automated measurement of right ventricular longitudinal strain. J Am Soc Echocardiogr 2022;35:609-19.
16. Lejeune S, Roy C, Ciocea V, et al. Right ventricular global longitudinal strain and outcomes in heart failure with preserved ejection fraction. J Am Soc Echocardiogr 2020;33:973-84.e2.
17. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of echocardiography and the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
18. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Scientific Document Committee of the European association of cardiovascular imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2013;14:611-44.
19. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. Eur Heart J Cardiovasc Imaging 2017;18:1342-3.
20. Praz F, Muraru D, Kreidel F, et al. Transcatheter treatment for tricuspid valve disease. EuroIntervention 2021;17:791-808.
21. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713. quiz 786-8.
22. Kuehne T, Saeed M, Gleason K, et al. Effects of pulmonary insufficiency on biventricular function in the developing heart of growing swine. Circulation 2003;108:2007-13.
23. Szabo G, Soos P, Bahrle S, et al. Adaptation of the right ventricle to an increased afterload in the chronically volume overloaded heart. Ann Thorac Surg 2006;82:989-95.
24. Sanz J, Sánchez-Quintana D, Bossone E, et al. Anatomy, function, and dysfunction of the right ventricle: JACC State-of-the-Art review. J Am Coll Cardiol 2019;73:1463-82.
25. Kundi H, Popma JJ, Cohen DJ, et al. Prevalence and outcomes of isolated tricuspid valve surgery Among Medicare Beneficiaries. Am J Cardiol 2019;123:132-8.
26. Prihadi EA, van der Bijl P, Dietz M, et al. Prognostic implications of right ventricular free wall longitudinal strain in patients with significant functional tricuspid regurgitation. Circ Cardiovasc Imaging 2019;12:e008666.
27. Ancona F, Melillo F, Calvo F, et al. Right ventricular systolic function in severe tricuspid regurgitation: prognostic relevance of longitudinal strain. Eur Heart J Cardiovasc Imaging 2021;22:868-75.
28. Bannehr M, Kahn U, Liebchen J, et al. Right ventricular longitudinal strain predicts survival in patients with functional tricuspid regurgitation. Can J Cardiol 2021;37:1086-93.
29. Akintoye E, Wang TKM, Nakhla M, et al. Quantitative echocardiographic assessment and optimal criteria for early intervention in asymptomatic tricuspid regurgitation. JACC Cardiovasc Imaging 2023;16:13-24.
30. Morris DA, Krisper M, Nakatani S, et al. Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study. Eur Heart J Cardiovasc Imaging 2017;18:212-23.
31. Dreyfus J, Audureau E, Bohbot Y, et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. Eur Heart J 2022;43:654-62.