Clinical Value of a Novel Three-Dimensional Echocardiography–Derived Index of Right Ventricle–Pulmonary Artery Coupling in Tricuspid Regurgitation

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Background: Echocardiographic surrogates of right ventricle–to–pulmonary artery (RV-PA) coupling have been reported to be associated with outcomes in patients with secondary tricuspid regurgitation (STR). However, pulmonary artery systolic pressure (PASP) is difficult to estimate using echocardiography in patients with severe STR. The aim of the present study was to evaluate the predictive power of a surrogate of RV-PA coupling obtained using right ventricular (RV) volumes measured on three-dimensional echocardiography.

Methods: One hundred eight patients (mean age, 73 ± 13 years; 61% women) with moderate or severe STR were included.

Results: At a median follow-up of 24 months (interquartile range, 2-48 months), 72 patients (40%) had reached the composite end point of death of any cause and heart failure hospitalization. RV-PA coupling was computed as the ratio between RV forward stroke volume (SV) (i.e., RV SV − regurgitant volume) and RV end-systolic volume (ESV). RV forward SV/ESV was significantly more related to the composite end point than RV ejection fraction (area under the curve, 0.85 [95% CI, 0.78-0.93] vs 0.73 [95% CI, 0.64-0.83], respectively; $P = .03$). A value of 0.40 was found to best correlate with outcome. On multivariate Cox regression, RV forward SV/ESV, tricuspid annular plane systolic excursion/PASP, and RV free wall longitudinal strain/PASP were all independently associated with the occurrence of the composite end point when added to a group of parameters including STR severity (severe vs moderate), atrial fibrillation, pulmonary arterial hypertension, right atrial volume, RV end-diastolic volume, and RV free wall longitudinal strain. RV forward SV/ESV < 0.40 (HR, 3.36; 95% CI, 1.49-7.56; $P < .01$) carried higher related risk than RV free wall longitudinal strain/PASP < −0.42%/mm Hg (HR, 3.1; 95% CI, 1.26-7.84; $P = .01$) and tricuspid annular plane systolic excursion/PASP < 0.36 mm/mm Hg (HR, 2.69; 95% CI, 1.29-5.58; $P = .01$). RV ejection fraction did not correlate independently with prognosis when added to the same group of variables.

Conclusions: RV forward SV/ESV is associated with the risk for death and heart failure hospitalization in patients with STR. (J Am Soc Echocardiogr 2023;■:■-■.)

Keywords: Three-dimensional echocardiography, Right ventricular function, Tricuspid regurgitation, Right ventricular–arterial coupling

Significant secondary tricuspid regurgitation (STR) is an independent predictor of morbidity and mortality,[1,2] and the extent of right ventricular (RV) dysfunction is strongly associated with the prognosis of patients with STR.[3-6] However, in patients with significant STR, the assessment of RV function can be challenging because the dilation and the change in the shape of the right ventricle may affect the

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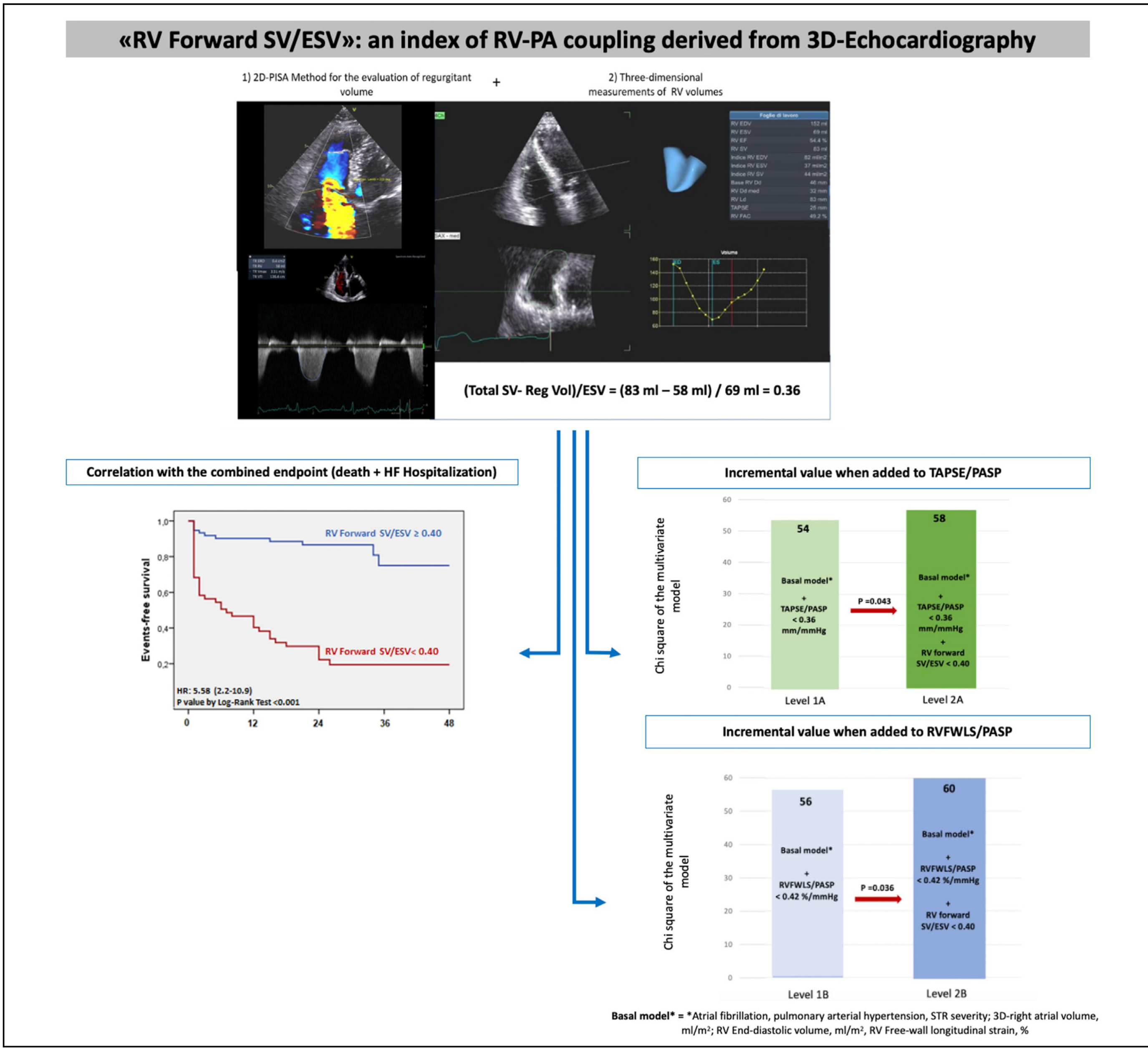

Central Illustration Computation of a 3D echocardiographic parameter of RV-PA coupling that does not require the estimate of pulmonary pressure and takes into account the amount of regurgitant flow and its incremental prognostic value in patients with STR. *EDV*, End-diastolic volume; *PA*, pulmonary artery; *PISA*, proximal isovelocity surface area.

accuracy of conventional echocardiography indexes evaluating both its longitudinal and global function.[7,8] Accordingly, three-dimensional (3D) imaging techniques (cardiac magnetic resonance, echocardiography, and cardiac computed tomography) are increasingly used to assess the RV ejection fraction (RVEF).[9-11]

However, because of its high load sensitivity, RVEF may not accurately reflect the actual RV systolic function in the presence of significant regurgitant volume (RegVol) and/or pulmonary hypertension.[12,13]

Recently, indexes of right ventricle–to–pulmonary artery (RV-PA) coupling have been proposed to evaluate RV function in patients with STR to overcome the load dependency of the conventional parameters of RV function. The ratio of tricuspid annular plane systolic excursion (TAPSE) to pulmonary artery systolic pressure (PASP) measured on echocardiography has been extensively studied,[13-15] and it is now recommended for the evaluation of patients with pulmonary hypertension.[13] This index has also been recently associated with outcomes in patients with severe STR.[13,14,16] Moreover, 3D parameters such as RVEF,[17] the ratio of RVEF to PASP,[18,19] and RV stroke volume (SV)/end-systolic volume (ESV) ratio[20] have shown prognostic value in different cohorts of right heart pathologies, including patients with STR[17] and pulmonary hypertension.[18,20] However, most of these indexes of RV-PA coupling rely on the

Abbreviations

3D = Three-dimensional

AUC = Area under the curve

Ea = Effective arterial elastance

Ees = End-systolic elastance

EROA = Effective regurgitant orifice area

ESP = End-systolic pressure

ESV = End-systolic volume

HF = Heart failure

HR = Hazard ratio

PASP = Pulmonary artery systolic pressure

RA = Right atrial

RegVol = Regurgitant volume

RV = Right ventricular

RVEF = Right ventricular ejection fraction

RVFWLS = Right ventricular free wall longitudinal strain

RV-PA = Right ventricle–to–pulmonary artery

STR = Secondary tricuspid regurgitation

SV = Stroke volume

TAPSE = Tricuspid annular plane systolic excursion

TR = Tricuspid regurgitation

TV = Tricuspid valve

estimation of PASP by Doppler echocardiography and on indexes of RV function, which are questionable in patients with severe STR.[21] Finally, none of them takes into account the effect of volume overload due to STR on RV functional assessment.[8,12,22]

To address these issues in the assessment of RV function in patients with either moderate or severe STR, we tested the association with the combined end point of death and hospitalization for heart failure (HF) of an index of RV-PA coupling obtained from RV volumes measured on 3D echocardiography, which is independent of PASP estimation and accounts for the severity of STR.

METHODS

Study Population

Consecutive patients referred for echocardiography with a first diagnosis of moderate or severe STR (significant STR) were included in a prospective observational study (FUTURE 3DECHO [The Functional Tricuspid Regurgitation by 3D Echocardiography Cooperative Study], ClinicalTrials.gov identifier NCT05747404).[23-26] This retrospective analysis of prospectively acquired data was approved by the ethics committee of Istituto Auxologico Italiano, IRCCS (record 2020_04_21_06, approved April 21, 2020). The need for patient written informed consent was waived because of the retrospective nature of the study. Exclusion criteria were poor image quality, presence of a pacemaker or an implantable cardioverter-defibrillator, organic tricuspid regurgitation (TR), highly irregular cardiac rhythm precluding the acquisition of multibeat 3D echocardiographic data sets with no stitching artifacts, and significant pulmonary regurgitation or stenosis.

Echocardiographic Analysis

Patients underwent standard two-dimensional and Doppler echocardiographic studies using Vivid E9/E95 scanners (GE Vingmed Ultrasound) equipped with M5S probes. Multibeat 3D data sets of the right atrium, the tricuspid valve (TV), and the right ventricle were acquired from the apical approach using 4V and 4Vc probes. Images were analyzed offline using the software packages included in EchoPAC 204 (GE Vingmed Ultrasound) by a single experienced researcher blinded to the patients' medical histories. Left ventricular volumes, ejection fraction, diastolic function, and PASP were assessed in all patients according to the most recent recommendations.[11,27] Conventional parameters of right atrial (RA) and RV size and function were measured from the focused RV apical view.[11] STR severity was graded as mild, moderate, or severe using the multiparametric approach, as recommended in current guidelines.[28-30] To reduce TR severity underestimation associated with the conventional proximal isovelocity surface area method,[31] the angle- and flow-corrected effective regurgitant orifice area (EROA) and RegVol were calculated.[32] Three-dimensional full-volume acquisitions of the right ventricle, TV, and right atrium were obtained from the RV-focused apical view using electrocardiographic gating over four to six consecutive cardiac cycles during a single breath hold.[33,34] In patients with atrial fibrillation, we used either multibeat (two or three consecutive beats in patients with fairly regular cardiac cycles) or single-beat 3D echocardiographic data set acquisitions and collected a minimum of three full-volume data sets. We excluded patients with large R-R variability compromising the acquisition of data set with temporal resolution higher than 19 volumes/sec. Gain settings were optimized, and the sector width and depth were adjusted to maximize temporal resolution. RV end-diastolic volume and end-ESV and RVEF were measured using 4D Auto RVQ. The geometry of the tricuspid annulus was evaluated using 4D Auto TVQ.[35] RV free wall longitudinal strain (RVFWLS) measurements were performed according to current recommendations.[36,37]

RV-PA coupling was estimated using the following parameters: TAPSE/PASP (mm/mm Hg), RVEF (percentage), RVFWLS/PASP (%/mm Hg), and RV forward SV/ESV. The latter parameter was derived by resolving the simplified formula of invasive RV-PA coupling[38,39] (i.e., RV end-systolic elastance [Ees]/effective arterial elastance [Ea] = [RV end-systolic pressure (ESP)/ESV]/[RV ESP/SV] = SV/ESV).[18] The novelty of the proposed index is the replacement of the total RV SV of the original formula with actual RV "anterograde" SV obtained by subtracting RegVol from total RV SV, thus obtaining the following formula: RV forward SV/ESV (Figure 1). In patients with atrial fibrillation, three to five consecutive heartbeats were averaged to obtain the final measurements of the study parameters.

Follow-Up and Study End Point

The primary end point was the occurrence of death for any cause and/or hospitalization for HF. Information concerning survival and hospitalization was obtained at regular intervals via (1) telephone interview with the patient or, if deceased, with family members; (2) contact with the patient's physician(s); and (3) review of electronic medical records of regular outpatient visits and hospital admission records. Mortality status was verified independently through the Social Security Death Index and death certificates. For patients without events, the date of the last contact was used for survival analysis. Assignment of clinical events was performed by physicians unaware of the patients' echocardiographic and clinical characteristics.

Reproducibility of RV and TR Volumes and RV Forward SV/ESV

Intra- and interobserver reproducibility of the RV volumes, TR volumes, and RV forward SV/ESV was tested using intraclass correlation coefficients and coefficients of variation by a reanalysis of the same beat of 32 qualitative random data sets by the same researcher (M.T.) and then a reanalysis by a different researcher (M.G.). The two investigators were blinded from the initial measurements.

HIGHLIGHTS

- TAPSE/PASP has been associated with prognosis in patients with STR.
- TAPSE/PASP relies on questionable Doppler PASP estimate in patients with severe STR.
- RV forward SV/ESV does not rely on PASP and accounts for RevVol.
- RV forward SV/ESV was associated with outcome in patients with significant STR.

Statistical Analysis

The normal distribution of continuous variables was tested using the Kolmogorov-Smirnov test. Continuous variables are reported as mean ± SD and were compared using Student's *t* test or the Mann-Whitney *U* test. Categorical variables are reported as counts and percentages and were compared using χ^2 or Fisher exact tests as appropriate. Receiver operating characteristic curves were used to assess the optimal cutoff values of TAPSE/PASP and RV forward SV/ESV, and the area under the curve (AUC) was derived for each. The De Long test was used to compare the AUCs of tested parameters.[40] A univariate Cox proportional hazards regression model was developed to identify the clinical and echocardiographic parameters that were independently associated with the composite end point. The results are shown as hazard ratios (HRs) with corresponding 95% CIs. To reduce multicollinearity, before multivariate Cox regression, preliminary analyses were performed using the variance inflation factor, considering values between 1 and 10 to indicate the absence of collinearity.[41] Taking into account collinearity and the clinical significance of the of two-dimensional and 3D echocardiography–derived variables, a basal group of echocardiographic variables was identified, and the incremental value for correlation with outcomes of TAPSE/PASP, RVFWLS/PASP, and RV forward SV/ESV was tested by adding their values to the basal group of variables. According to the results of the collinearity analyses, to avoid overfitted analysis, two distinct nested models were built. The change in overall log likelihood ratio χ^2 was used to assess the increase in the predictive power of the models.[42] Kaplan-Meier curves were used to estimate event-free survival rates, and differences between groups were analyzed using the log-rank test. Statistical analyses were performed using SPSS version 28 (SPSS) and R version 4.0.1 (R Foundation for Statistical Computing). A two-sided significance level of $P < .05$ was considered statistically significant.

RESULTS

A total of 210 patients were screened. From this cohort, we excluded 30 patients (14%; Figure 2). Central Illustration summarizes the method and the most relevant findings. Table 1 summarizes the main characteristics of the study population. All patients had at least

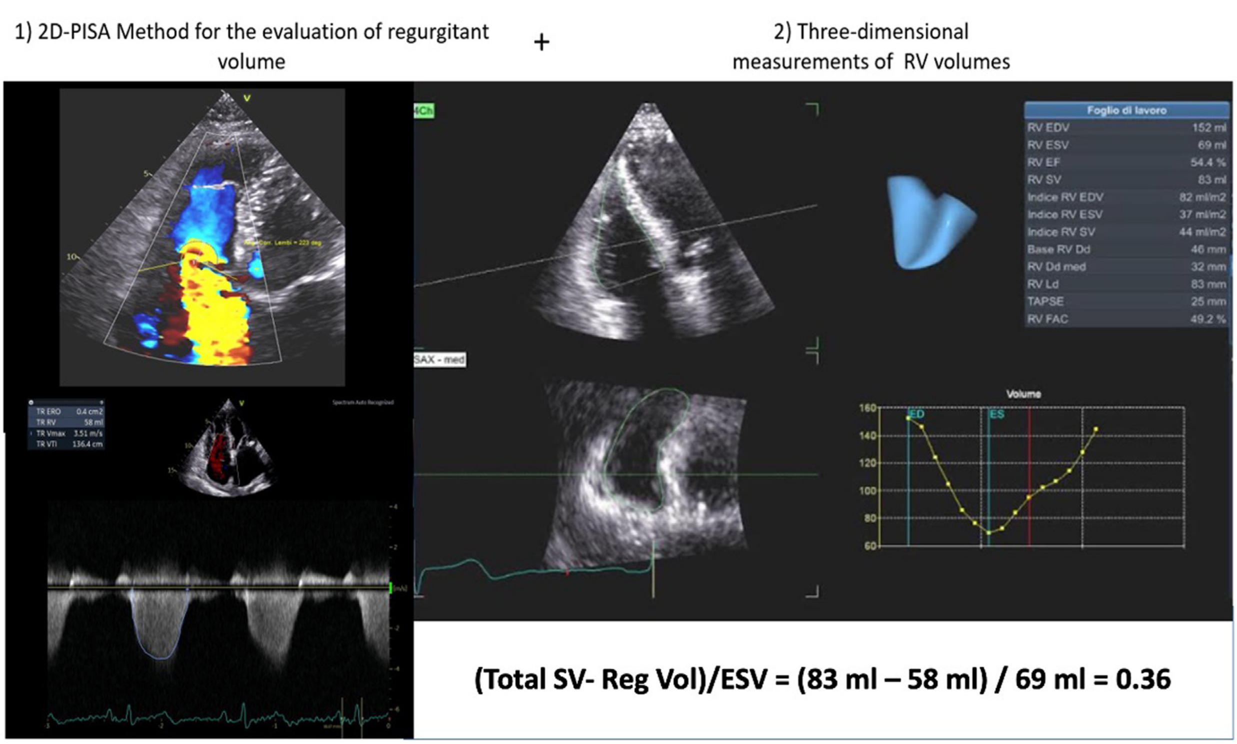

Figure 1 Echocardiographic assessment of RV forward SV/ESV. The total SV of the right ventricle measured using 3D echocardiography was corrected by subtracting the RegVol obtained from the corrected proximal isovelocity surface area (PISA) equation (*top left and bottom left*), thus obtaining the 3D echocardiographic index of RV-PA coupling. *2D*, Two-dimensional; *Dd med*, midventricular transversal diameter; *EDV*, end-diastolic volume; *EF*, ejection fraction; *ERO*, effective regurgitant orifice; *FAC*, fractional area change; *Ld*, length; *Vmax*, peak velocity TR jet; *VTI*, velocity-time integral.

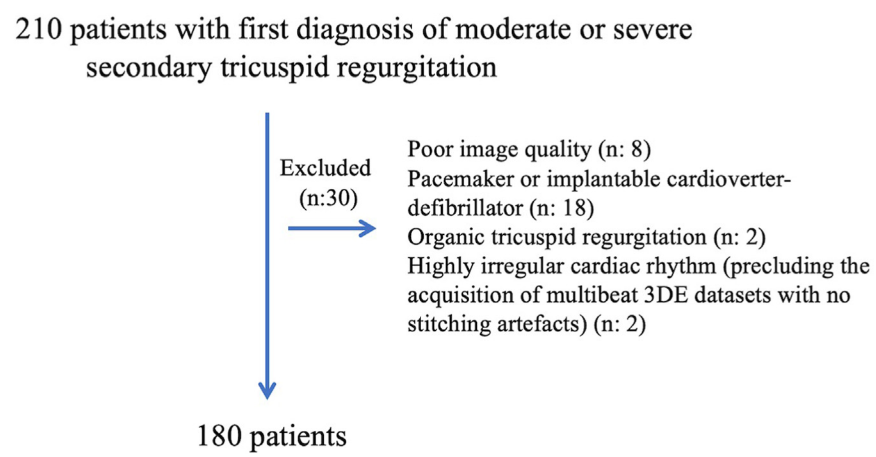

Figure 2 Patient selection flowchart. *3DE*, Three-dimensional echocardiographic.

moderate STR. STR was severe in 41% of our patients. Almost 50% of the included patients had atrial fibrillation at the time of evaluation. Only 5% of the patients had left ventricular ejection fractions <40%.

Patients who developed the combined end point showed more severe STR, a higher degree of TV remodeling, larger RA and RV volumes, and lower values of RV functional parameters than patients who did not (Table 1). After a median follow-up period of 24 months (interquartile range, 2-48 months), 72 patients (40%) reached the primary end point, and 64 (36% of the whole population) had at least one hospitalization for HF. On receiver operating characteristic analysis, the threshold value that provided the largest AUCs for RV forward SV/ESV was 0.40 (sensitivity, 80%; specificity, 80%). The corresponding threshold value for TAPSE/PASP and RVFWLS/PASP in our population were, respectively, 0.36 mm/mm Hg (sensitivity, 75%; specificity, 74%) and −0.42%/mm Hg (sensitivity, 72%; specificity, 65%). RV forward SV/ESV showed a statistically significantly larger AUC than RVEF (0.79 [95% CI, 0.65-0.89] vs 0.63 [95% CI, 0.49-0.77], P = .01). Higher AUC was observed also when comparing RV forward SV/ESV with TAPSE/PASP (AUC, 0.68; 95% CI, 0.59-0.84) and RVFWLS/PASP (AUC, 0.71; 95% CI, 0.62-0.90; Figure 3). The results of Cox regression univariate analysis are shown in Table 2. The correlates of the primary end point were found to be reduced functional capacity (i.e., New York Heart Association functional class III or IV vs I or II), permanent atrial fibrillation, pulmonary arterial hypertension, STR severity, RA and RV volumes, RV functional parameters, the tested indices of RV-PA coupling, and RV forward SV. The correlation with outcomes of the RV forward SV, alone, was weaker than that of RV forward SV/ESV (HR, 0.97 [95% CI, 0.96-0.98; $P < .001$] vs 0.10 [95% CI, 0.03-0.16; $P < .001$]).

Taking into account the collinearity and the clinical relevance of the two-dimensional and 3D echocardiography–derived variables, different models of multivariable analysis were developed (Table 3, Supplemental Table 1). When added to a basal group of echocardiographic and clinical variables including STR severity (severe vs moderate), atrial fibrillation, pulmonary arterial hypertension, RA and RV volumes, and RVFWLS, RV forward SV/ESV < 0.40, TAPSE/PASP < 0.36 mm/mm Hg, and RVFWLS/PASP < −0.42%/mm Hg were independently associated with the occurrence of the primary end point (Table 3). RV forward SV/ESV < 0.40 (HR, 3.36; 95% CI, 1.49-7.56; $P < .01$) carried higher related risk than RVFWLS/PASP < −0.42%/mm Hg (HR, 3.1; 95% CI, 1.26-7.84; $P = .01$) and TAPSE/PASP < 0.36 mm/mm Hg (HR, 2.69; 95% CI, 1.29-5.58; $P = .01$). Conversely, RVEF was not independently associated with the combined end point (HR, 0.98; 95% CI, 0.95-1.02; $P = .32$) when added to the same group of variables. Supplemental Table 1 shows the results of the Cox regression analysis using TAPSE/PASP, RVFWLS/PASP, and RV forward SV/ESV as continuous variables.

On nested regression analysis, RV forward SV/ESV had incremental value in correlating with outcomes when added to different models including TAPSE/PASP and RVFWLS/PASP (Figure 4).

In the whole study population, patients with RV forward SV/ESV < 0.40 had a 5.6-fold increased risk for experiencing the combined end point (Figure 5A) and a 2.9-fold increased risk for dying (Figure 5B). A value of RV forward SV/ESV of <0.40 significantly diverged the risk for the combined end point both in patients with TAPSE/PASP ≥ 0.36 mm/mm Hg and in those with TAPSE/PASP < 0.36 (Figure 6A and B). In addition, RV forward SV/ESV < 0.40 identified patients at risk both among patients with moderate STR (EROA < 0.4 cm^2), who had 5.0-fold increased risk for the combined end point, and among those with severe STR (EROA ≥ 0.4 cm^2), who had 2.5-fold increased risk (Figure 6C and D). Both TAPSE/PASP and RVFWLS/PASP showed a similar pattern. The more severe was STR, the lower was the correlation of indices of RV-PA coupling with outcomes (Supplemental Table 2).

Patients with RV forward SV/ESV < 0.40 showed more severe STR, larger RV and RA volumes, worse RV function, and higher PASP than patients with RV forward SV/ESV > 0.40 (Supplemental Table 3).

The intraclass correlation coefficients of the intra- and interobserver reproducibility for RV volumes, STR RegVol, and RV forward SV/ESV were excellent, ranging from 0.961 to 0.995 and from 0.943 and 0.98, respectively (Supplementary Table 4).

DISCUSSION

The present study is the first to report the association with the combined end point of death and hospitalization for HF of an

Table 1 Clinical and echocardiographic characteristics of the whole study population and of patients who either met or did not meet the primary end point of all-cause death and hospitalization for HF

	Whole population (*n* = 180)	Events (*n* = 72)	No events (*n* = 108)	*P*
Clinical factors				
Age, y	73.3 ± 13.0	72.4 ± 15.4	73.9 ± 12.4	.45
Gender, female	109 (61)	43 (59.7)	66 (61.1)	.49
NYHA functional class III or IV	75 (41)	43 (54)	32 (32)	.01
Body surface area, m^2	1.52 ± 0.63	1.43 ± 0.67	1.57 ± 0.59	.15
Heart rate, beats/min	76 ± 18	77 ± 12	75 ± 21	.59
Systolic blood pressure, mm Hg	129 ± 22	126 ± 23	131 ± 21	.20
Diastolic blood pressure, mm Hg	75 ± 13	73 ± 12	77 ± 13	.12
Diabetes	31 (17)	9 (13)	22 (20)	.24
Arterial hypertension	58 (32)	17 (23.6)	41 (38)	.031
Chronic obstructive pulmonary disease	22 (12)	7 (9.7)	15 (13.9)	.276
Ischemic heart disease	26 (14)	10 (13.9)	16 (14.8)	.521
Previous valve surgery	4 (2)	1 (1.4)	3 (2.8)	.470
Atrial fibrillation	85 (47)	48 (67)	37 (34)	<.001
Precapillary pulmonary hypertension	54 (30)	38 (33)	16 (15)	.01
Left heart characteristics				
LV ejection fraction, %	61 ± 9	61 ± 9	60 ± 9	.80
LV ejection fraction < 40%	10 (5)	3 (4.1)	7 (6.5)	.22
Left atrial maximal volume, mL/m^2	51 ± 2	49 ± 21	53 ± 22	.51
TR severity				
Severe TR	73 (40.6)	44 (61.1)	29 (26.9)	<.001
2D vena contracta, cm	0.62 ± 0.35	0.81 ± 0.37	0.46 ± 0.23	<.001
3D vena contracta area, cm^2	1.05 ± 0.7	1.34 ± 0.92	0.83 ± 0.54	<.001
EROA, cm^2	0.34 (0.29-0.39)	0.47 (0.29-0.61)	0.21 (0.1-0.27)	.002
EROA > 0.4 cm^2	40 (22)	27 (37)	13 (12)	<.001
RegVol, %	42.7 ± 25.0	57.5 ± 21.3	28 ± 18.6	<.001
TV remodeling				
Tenting height, mm	14.1 ± 5.3	17 ± 5.4	10.9 ± 5.7	<.001
Tenting volume, mL	4.0 ± 1.8	4.2 ± 2	3.9 ± 1.7	.39
Tricuspid annular diameter, mm	41 ± 6.9	42.8 ± 6.9	40 ± 6.8	.01
End-diastolic tricuspid annular area, cm^2	12.7 ± 3.4	13.4 ± 3.6	12.2 ± 3.2	.04
End-systolic tricuspid annular area, cm^2	10.5 ± 3.2	10.9 ± 3.4	10.2 ± 2.8	.29
Right atrium				
3D maximum volume, mL/m^2	58.4 ± 29.4	68.7 ± 35	52.6 ± 24.1	.001
3D minimum volume, mL/m^2	49.4 ± 23.8	58.8 ± 24.1	38.8 ± 18.6	<.001
Estimated RA pressure, mm Hg	6.3 ± 3.2	6.3 ± 2.8	6.4 ± 3.4	.86
Right ventricle				
End-diastolic basal diameter, mm/m^2	26 ± 5	29 ± 5	24 ± 5	<.001
End-diastolic volume, mL/m^2	86 ± 38	104 ± 45	73 ± 26	<.001
ESV, mL/m^2	49 ± 30	63 ± 38	39 ± 17	<.001
SV, mL/m^2	36 ± 13	41 ± 13	34 ± 12	.002
TAPSE, cm	1.7 ± 0.6	1.7 ± 0.4	1.7 ± 0.7	.74
RVFWLS, %	−19.2 ± 5.3	−17.5 ± 4.9	−20.4 ± 5.2	.001
RVEF, %	45.2 ± 10.1	41.8 ± 10.9	47.6 ± 8.7	<.001
PASP, mm Hg	55.7 ± 23.4	60.5 ± 26.9	42.3 ± 16.0	<.001
RV-PA coupling				
TAPSE/PASP, mm/mm Hg	0.42 ± 0.25	0.32 ± 0.17	0.47 ± 0.27	<.001

(*Continued*)

Table 1 (*Continued*)

	Whole population (n = 180)	Events (n = 72)	No events (n = 108)	P
RVFWLS/PASP, (−%)/mm Hg	0.47 ± 0.24	0.36 ± 0.20	0.56 ± 0.22	<.001
RV forward SV/ESV	0.45 ± 0.31	0.29 ± 0.22	0.59 ± 0.29	<.001

2D, Two-dimensional; *LV*, left ventricular; *NYHA*, New York Heart Association.
Data are expressed as mean ± SD, number (percentage), or median (IQR).

echocardiographic parameter that is derived from the invasive formula of RV-PA coupling, does not rely on the Doppler echocardiographic estimate of PASP, and considers the amount of RegVol in patients with significant STR.

The main findings of our study can be summarized as follows: (1) in patients with significant STR, both STR severity and echocardiographic RV-PA coupling indexes are strongly and independently associated with the occurrence of the composite end point of all-cause death and hospitalization for HF, and (2) a new 3D echocardiographic index obtained by correcting the formula of invasive coupling for the RegVol of STR (i.e., RV forward SV/ESV) showed a closer association with outcome compared with other echocardiographic indexes of RV-PA coupling, such as TAPSE/PASP, RVEF, and RVFWLS/PASP.

The prognosis of patients with significant STR is strongly influenced by the extent of RV dysfunction.[3,4,43-45] Both cardiac conditions inducing the onset of STR (i.e., left heart pathologies, pulmonary artery hypertension, RV cardiomyopathies, etc.) and the volume overload associated with progressive STR may lead to maladaptive RV remodeling.[46] Although echocardiography plays the most important role in the follow-up of patients with STR and in their selection for TV interventions, the best way to assess RV function by echocardiography in patients with significant STR remains an open question.[47] Established echocardiographic parameters of RV dysfunction, such as TAPSE, rely on geometric assumptions, are angle and load dependent, and reflect the change in the size of the RV cavity only along the longitudinal axis and without considering the direction (anterograde or retrograde) of flow. Although parameters of RV function obtained from myocardial deformation imaging (i.e., RV longitudinal strain parameters) are less angle dependent,[48,49] they maintain load dependency. Three-dimensional echocardiography allows the measurement of RV volumes and RVEF by considering all the directions of the myocardial displacement and without geometric assumptions about the shape of the right ventricle, therefore better representing RV global function.[50] However, RVEF is heavily dependent on RV loading conditions.[51,52]

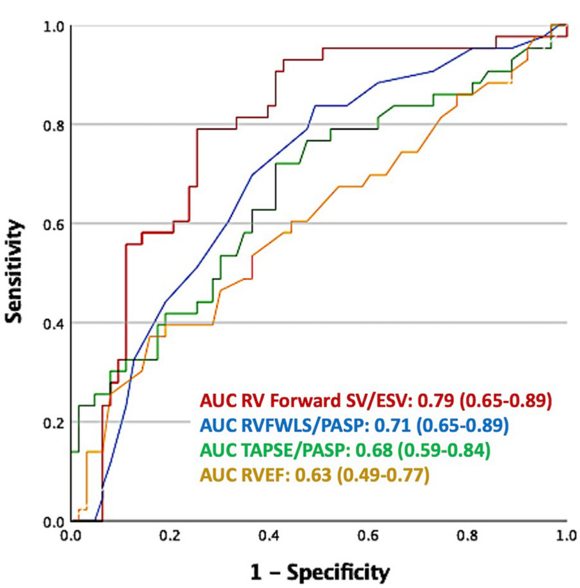

Figure 3 Comparison of the AUCs of the various echocardiographic indexes of RV-PA coupling.

To overcome the load dependence of the conventional echocardiographic parameters used to assess RV function, the ratio between parameters of RV function and Doppler-estimated PASP has been proposed in different clinical scenarios as surrogates of the invasively determined RV-PA coupling.[53] So far, only TAPSE/PASP has been tested in patients with STR, and it was associated with outcomes.[14,16] However, patients with significant STR pose unique challenges in using either TAPSE/PASP or RVFWLS/PASP ratio. The noninvasive estimation of PASP by echocardiography is the summation of the Doppler-derived RV-RA systolic pressure gradient and the mean RA pressure obtained from inferior vena cava interrogation. In patients with severe STR, characterized by large EROA, a low-flow state occurs, and therefore the two basic assumptions of the Bernoulli law (i.e., that the velocity is dependent "only" on pressure and that the proximal velocity [preorifice] is much less than the distal velocity and therefore can be ignored) are no longer valid.[54,55] Another issue when STR is severe and rapid equalization of the RV and RA pressures (large RA V waves) occurs, is that RA pressure is much more dynamic, and it is grossly underestimated using the conventional "static" noninvasive parameters. All previous considerations make the echocardiographic assessment of PASP quite inaccurate in patients with severe STR.[21] In addition, TAPSE may not accurately reflect RV function in patients with severe pressure and volume overload[56] and after cardiac surgery.[57]

The gold-standard measurement of RV function adaptation to changing loading conditions, or ventricular-vascular coupling, is the ratio between Ees (i.e., a measure of RV contractility) and Ea (i.e., a measure of pulmonary arterial afterload).[58,59] Ees has been approximated by the ratio between ESP and RV ESV, and Ea has been approximated as the ratio between ESP and RV SV. Measurements of RV volumes can be obtained by cardiac magnetic resonance imaging and, more recently, by 3D echocardiography; accurate measurements of RV pressures in patients with STR require right heart catheterization.[21]

As the Ees/Ea ratio (ESP/ESV)/(ESP/SV) has a common term (i.e., ESP), it can be simplified as the ratio of SV to ESV. The ratio of left ventricular SV to ESV has been reported as an index of ventriculoarterial coupling in patients with left-sided disease and HF.[60] For the "right side," the use of RV volumes for noninvasive assessment of RV-PA coupling has been invasively validated by Aubert *et al.*[20] Its

Table 2 Univariate Cox regression analysis for correlates of the composite end point (all-cause death and hospitalization for HF)

Factor	HR (95% CI)	*P*
Clinical factors		
Age	1.00 (0.98-1.02)	.76
NYHA functional class III or IV	1.3 (1.01-1.69)	.04
Body surface area	0.99 (0.92-1.08)	.94
Heart rate	1.01 (0.99-1.02)	.17
Systolic blood pressure	0.99 (0.98-1.02)	.21
Atrial fibrillation	2.28 (1.39-3.74)	<.01
Pulmonary arterial hypertension	1.20 (1.01-1.42)	.03
Diabetes	0.73 (0.31-1.71)	.47
Arterial hypertension	0.64 (0.37-1.09)	.11
Chronic obstructive pulmonary disease	0.94 (0.43-2.05)	.87
Ischemic heart disease	0.58 (0.21-1.59)	.29
Previous valve surgery	0.88 (0.53-1.51)	.64
Left heart characteristics		
LV ejection fraction	0.99 (0.97-1.02)	.71
Left atrial maximal volume	0.99 (0.98-1.01)	.77
Elevated LV filling pressures	0.65 (0.37-1.03)	.07
TR severity		
Severe TR	3.6 (2.2-5.8)	<.01
2D vena contracta	1.18 (1.1-1.2)	<.01
3D vena contracta area	1.51 (1.2-2.3)	<.01
EROA	1.4 (1.1-1.7)	<.01
EROA ≥ 0.4 cm^2	3.02 (1.8-4.9)	<.01
Regurgitant fraction	1.04 (1.03-1.05)	<.01
TV remodeling		
Tenting height	1.12 (1.05-1.19)	<.01
Tenting volume	1.11 (0.95-1.29)	.19
Tricuspid annular diameter	1.04 (1.00-1.07)	.03
End-diastolic tricuspid annular area	1.06 (0.99-1.44)	.09
End-systolic tricuspid annular area	1.06 (0.98-1.44)	.12
Right atrium		
3D RA maximum volume	1.01 (1.01-1.03)	<.01
3D RA minimum volume	1.01 (1.01-1.02)	<.01
Estimated RA pressure	1.01 (0.93-1.09)	.82
Right ventricle		
End-diastolic basal diameter	1.08 (1.04-1.13)	<.001
End-diastolic volume	1.01 (1.01-1.02)	<.001
ESV	1.01 (1.01-1.02)	<.001
SV	1.03 (1.01-1.04)	.01
Forward SV	0.97 (0.96-0.98)	<.001
PASP	1.02 (1.01-1.03)	<.001
TAPSE	0.96 (0.88-0.97)	.02
RVFWLS	0.93 (0.88-0.97)	<.001
RVEF	0.98 (0.94-0,97)	.004
RV-PA coupling		
TAPSE/PASP	0.07 (0.01-0.27)	<.01
TAPSE/PASP < 0.36	1.76 (1.10-1.8)	.018
RVFWLS/PASP	0.042 (0.01-0.17)	<.001
RV forward SV/ESV	0.10 (0.03-0.16)	<.001
RV forward SV/ESV < 0.40	7.4 (3.78-14.45)	<.001

2D, Two dimensional; *LV*, left ventricular; *NYHA*, New York Heart Association.

prognostic power has been explored in several cohorts of patients with pulmonary hypertension,[20,22,52,61] and some cutoff values associated with mortality have been reported in patients with RV SV/ESV < 0.515 by Vanderpool *et al.*[12] and <0.534 by Brewis *et al.*[62] However, no study has addressed the value of this index of RV-PA coupling in patients with significant STR. The obvious advantage of the SV/ESV ratio is that it relies only on volume measurements, thus allowing a reliable noninvasive estimate of RV-PA coupling in patients with significant TR by overcoming the need to measure PASP. This formula relies only on the assumption that ESP in the right ventricle and in the pulmonary artery are not different. Accordingly, we excluded patients with significant RV outflow tract obstruction or pulmonary valve stenosis. In addition, to take into account the peculiar hemodynamics of TR and the severity of STR, we obtained the actual amount of SV that is ejected into the pulmonary artery during each cardiac beat by subtracting the tricuspid RegVol from the total RV SV to obtain the RV forward SV.

The SV/ESV ratio is mathematically related to RVEF (e.g., $SV/ESV = RVEF/[1 - RVEF]$). Accordingly, it could have the same prognostic power of RVEF. However, in patients with pulmonary hypertension, it has been demonstrated that SV/ESV does not have a linear relationship with RVEF. Moreover, a wide range of SV/ESV ratios have been found for any RVEF, thus demonstrating an increased resolution of the SV/ESV ratio for prognostic stratification even in patients with a relatively normal RVEF.[12] Moreover, the SV/ESV ratio has been demonstrated to be less sensitive to volume changes than RVEF, and this can represent an additional advantage in patients with STR.[12,52]

Study Limitations

The present is a retrospective analysis of prospectively enrolled patients who were included in the study according to the presence of significant

Table 3 Four models of multivariable Cox regression analysis for correlates of the composite end point of all-cause death and hospitalization for HF in STR

Factor	HR (95% CI)	*P*
Model 1		
Severe TR (vs moderate)	3.79 (1.79-8.06)	<.01
Atrial fibrillation (yes vs no)	2.84 (1.29-6.24)	.01
Pulmonary arterial hypertension (yes vs no)	1.33 (1.04-1.71)	.03
3D RA maximum volume	0.99 (0.98-1.01)	.79
RV end-diastolic volume	1.00 (0.99-1.01)	.61
RVFWLS, %	0.96 (0.91-1.02)	.17
TAPSE/PASP < 0.36 mm/mm Hg	**2.69 (1.29-5.58)**	**.01**
Model 2		
Severe TR (vs moderate)	3.93 (1.82-8.47)	<.01
Atrial fibrillation (yes vs no)	4.11 (1.81-9.37)	<.01
Pulmonary arterial hypertension (yes vs no)	1.37 (1.06-1.76)	.02
RV end-diastolic volume	1.00 (0.99-1.04)	.76
RVFWLS, %	0.97 (0.92-1.04)	.45
RV forward SV/ESV < 0.40	**3.36 (1.49-7.56)**	**<.01**
Model 3		
Severe TR (vs moderate)	4.51 (2.12-9.61)	<.01
Atrial fibrillation (yes vs no)	3.20 (1.45-7.08)	<.01
Pulmonary arterial hypertension (yes vs no)	1.32 (1.02-1.71)	.04
RV end-diastolic volume	1.00 (0.99-1.01)	.54
RVFWLS, %	0.95 (0.89-1.00)	.07
RVEF	**0.98 (0.95-1.02)**	**.32**
Model 4		
Severe TR (vs moderate)	3.82 (1.76-8.32)	<.01
Atrial fibrillation (yes vs no)	2.94 (1.32-6.53)	.01
Pulmonary arterial hypertension (yes vs no)	1.27 (0.98-1.64)	.07
RV end-diastolic volume	1.00 (0.99-1.01)	.53
RVFWLS, %	0.99 (0.92-1.06)	.74
RVFWLS/PASP < −0.42%/mm Hg	**3.09 (1.26-7.84)**	**.01**

ESV, end systolic volume; *NYHA*, New York Heart Association; *PASP*, pulmonary arterial systolic pressure; *RV*, right ventricle; *RVEF*, right ventricular ejection fraction; *SV*, stroke volume; *TAPSE*, tricuspid annular plane systolic excursion.

STR during clinically indicated echocardiography and had good image quality. However, this study is a proof of concept. The feasibility of the RV forward SV/ESV ratio in the general population of patients with significant STR remains to the established. Similarly, the proposed threshold value of 0.4 for the RV forward SV/ESV ratio needs external validation in multicenter prospective studies.

The RV forward SV/ESV has not been validated against invasive indices of RV-PA coupling (i.e., Ees/Ea). However, the use of 3D echocardiographic RV volumes for the noninvasive assessment of RV-PA coupling was invasively validated by Aubert *et al.*,[20] and the only change we made was the subtraction of RegVol from total RV SV to take into account the severity of the regurgitation.

Although forward SV/ESV, as a parameter of RV-PA coupling, does not require the estimation of PASP, it remains a surrogate of RV-PA coupling, and this index does not pretend to be its exact quantitative assessment. The novelty of our study was to move beyond RVEF and TAPSE in patients with STR, to try to account for the peculiar hemodynamics of this heart valve disease. Furthermore, the computation of forward SV/ESV does not require more acquisitions or time than the computation of RVEF.

Finally, the use of the combined end point including HF hospitalization in such a selected population may lead to the inclusion of events occurring early during follow-up.

CONCLUSION

Our results should not discourage the evaluation of other RV functional parameters such as RVEF but, on the contrary, should encourage (1) a comprehensive multiparametric evaluation that should also be repeated during follow-up to identify the stage in which the conventional RV function parameters are still normal and patients have RV-PA decoupling and (2) the routine use of 3D assessment of RV volumes in this cohort. Patients with limited acoustic windows that prevent the acquisition of good-quality 3D data sets can be studied using cardiac magnetic resonance imaging to obtain the same index. Studies with larger cohorts of patients and longer follow-up may be needed to confirm our results.

REVIEW STATEMENT

Given his role as JASE Associate Editor, Luigi P. Badano, MD, PhD, had no involvement in the peer review of this article and has no

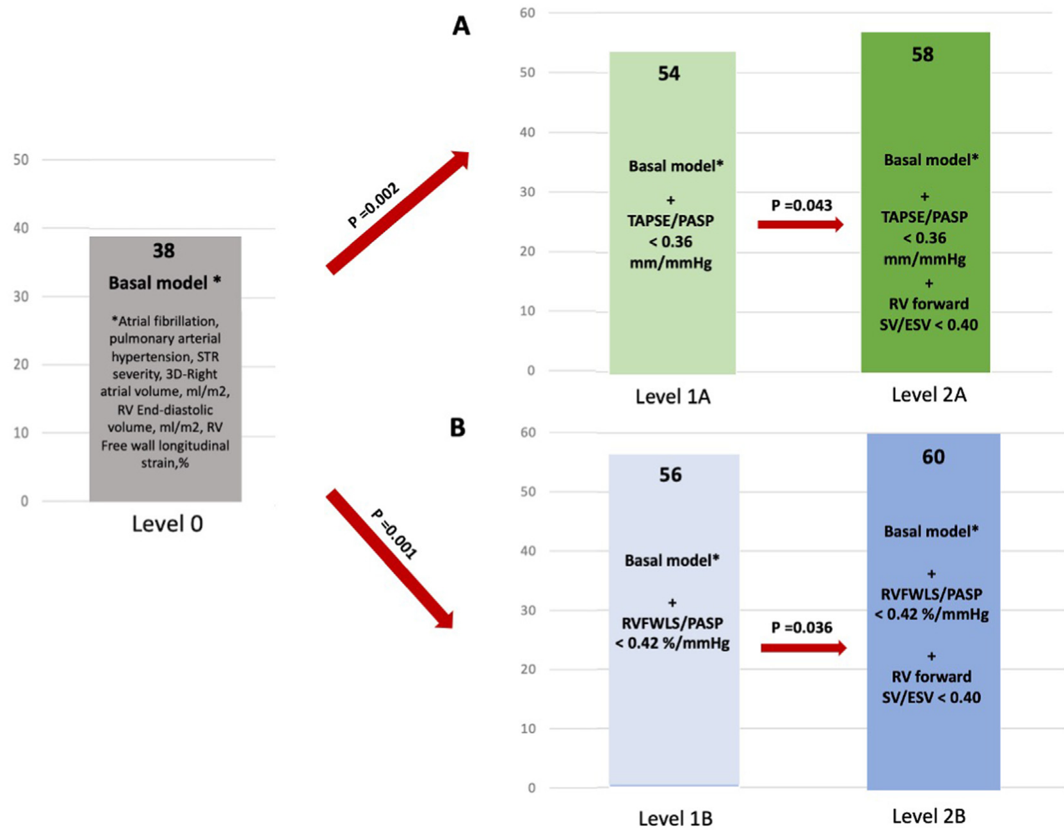

Figure 4 Nested regression models showing the incremental correlation with outcomes of the tested indexes of RV-PA coupling, on top of the basal model including permanent atrial fibrillation, pulmonary arterial hypertension, TR severity (severe vs moderate), RA and RV volumes, and RVFWLS. **(A)** Increase of the χ^2 statistic of the basal model after adding TAPSE/PASP (level 1A) and after adding RV forward SV/ESV to model 1A (level 2A). **(B)** Increase of the χ^2 statistic of the basal model after adding RVFWLS/PASP (level 1B) and after adding RV forward SV/ESV to model 1B (level 2B).

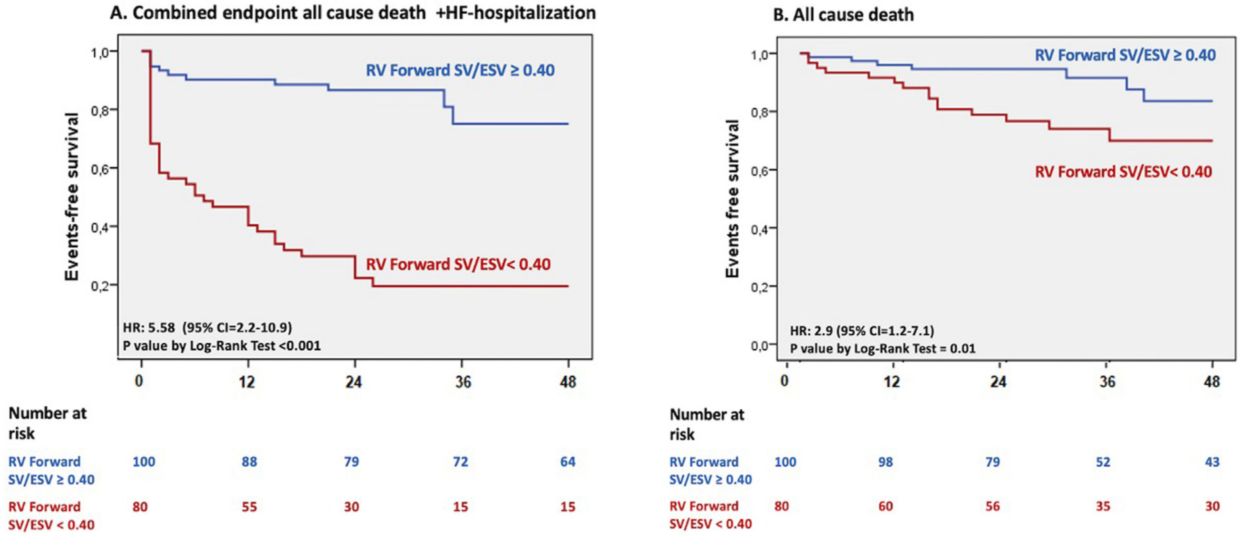

Figure 5 Event-free survival (combined end point in **A** and death of any cause in **B**) in patients with significant STR and RV forward SV/ESV ratio >0.40 or <0.40.

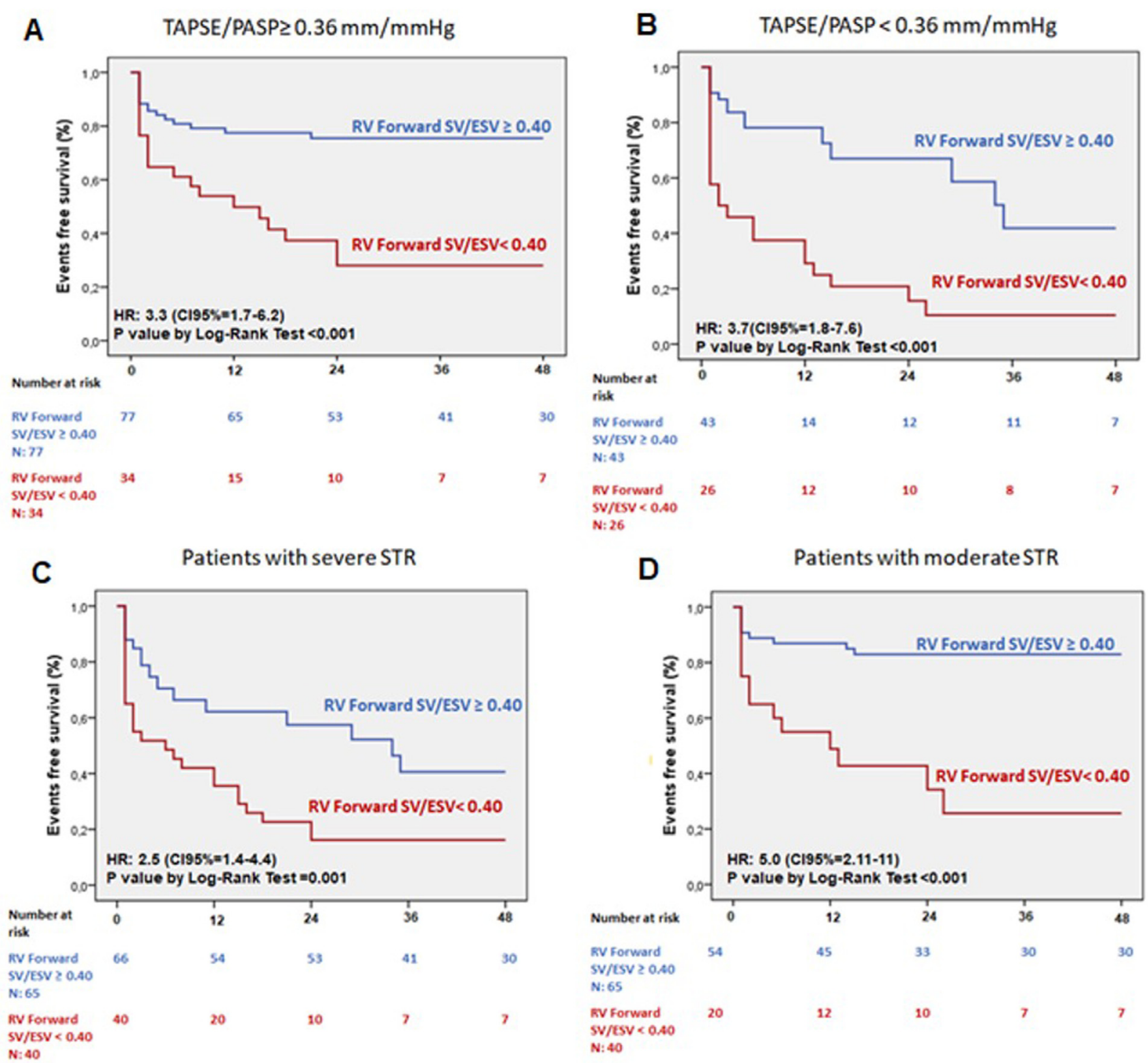

Figure 6 Event-free survival for the combined end point of hospitalization for HF and all-cause death according to RV forward SV/ESV >0.40 or <0.40 in patients with significant TR and TAPSE/PASP ≥ 0.36 mm/mm Hg **(A)** or TAPSE/PASP < 0.36 mm/mm Hg **(B)** and in patients with severe **(C)** or moderate **(D)** STR.

access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Kian Keong Poh, MBBChir.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2023.06.014.

REFERENCES

1. Wang N, Fulcher J, Abeysuriya N, et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. Eur Heart J 2019;40:476-84.
2. Offen S, Playford D, Strange G, et al. Adverse prognostic Impact of even mild or moderate tricuspid regurgitation: insights from the National Echocardiography Database of Australia. J Am Soc Echocardiogr 2022;35:810-7.
3. Itelman E, Vatury O, Kuperstein R, et al. The association of severe tricuspid regurgitation with poor survival is Modified by right ventricular pressure and function. J Am Soc Echocardiogr 2022;35:1028-36.
4. Dietz MF, Goedemans L, Vo NM, et al. Prognostic implications of significant isolated tricuspid regurgitation in patients with atrial fibrillation without left-sided heart disease or pulmonary hypertension. Am J Cardiol 2020;135:84-90.
5. Bannehr M, Kücken T, Ulrike K, et al. Prognostic implications of a Novel Algorithm to Grade secondary tricuspid regurgitation. J Am Soc Echocardiogr 2021;34:1316-7.

6. Fortuni F, Dietz MF, Prihadi EA, et al. Ratio between vena Contracta width and tricuspid annular diameter: prognostic value in secondary tricuspid regurgitation. J Am Soc Echocardiogr 2021;34:944-54.
7. 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.
8. Zhao H, Kang Y, Pickle J, et al. Tricuspid annular plane systolic excursion is dependent on right ventricular volume in addition to function. Echocardiography 2019;36:1459-66.
9. Surkova E, Muraru D, Iliceto S, et al. The use of multimodality cardiovascular imaging to assess right ventricular size and function. Int J Cardiol 2016;214:54-69.
10. Badano LP, Addetia K, Pontone G, et al. Advanced imaging of right ventricular anatomy and function. Heart 2020;106:1469-76.
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. J Am Soc Echocardiogr 2015;28:1-39.e14.
12. Vanderpool RR, Rischard F, Naeije R, et al. Simple functional imaging of the right ventricle in pulmonary hypertension: can right ventricular ejection fraction be improved? Int J Cardiol 2016;223:93-4.
13. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;44:792-3.
14. Brener MI, Lurz P, Hausleiter J, et al. Right ventricular-pulmonary arterial coupling and afterload reserve in patients undergoing transcatheter tricuspid valve repair. J Am Coll Cardiol 2022;79:448-61.
15. Tello K, Wan J, Dalmer A, et al. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. Circ Cardiovasc Imaging 2019;12:e009047.
16. Fortuni F, Butcher SC, Dietz MF, et al. Right ventricular-pulmonary arterial coupling in secondary tricuspid regurgitation. Am J Cardiol 2021;148:138-45.
17. Orban M, Wolff S, Braun D, et al. Right ventricular function in transcatheter edge-to-edge tricuspid valve repair. JACC Cardiovasc Imaging 2021;14:2477-9.
18. Li Y, Guo D, Gong J, et al. Right ventricular function and its coupling with pulmonary circulation in precapillary pulmonary hypertension: a three-dimensional echocardiographic study. Front Cardiovasc Med 2021;8:690606.
19. Vitarelli A, Capotosto L, Mangieri E, et al. A novel index of right ventriculoarterial coupling in adult patients with repaired tetralogy of fallot using three-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr 2023;36:341-3.
20. Aubert R, Venner C, Huttin O, et al. Three-dimensional echocardiography for the assessment of right ventriculo-arterial coupling. J Am Soc Echocardiogr 2018;31:905-15.
21. Lurz P, Orban M, Besler C, et al. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. Eur Heart J 2020;41:2785-95.
22. Trip P, Kind T, van de Veerdonk MC, et al. Accurate assessment of load-independent right ventricular systolic function in patients with pulmonary hypertension. J Heart Lung Transplant 2013;32:50-5.
23. Guta AC, Badano LP, Tomaselli M, et al. The pathophysiological link between right atrial remodeling and functional tricuspid regurgitation in patients with atrial fibrillation: a three-dimensional echocardiography study. J Am Soc Echocardiogr 2021;34:585-94.e1.
24. Florescu DR, Muraru D, Florescu C, et al. Right heart chambers geometry and function in patients with the atrial and the ventricular phenotypes of functional tricuspid regurgitation. Eur Heart J Cardiovasc Imaging 2021;23:930-40.
25. Muraru D, Addetia K, Guta AC, et al. Right atrial volume is a major determinant of tricuspid annulus area in functional tricuspid regurgitation: a three-dimensional echocardiographic study. Eur Heart J Cardiovasc Imaging 2021;22:660-9.
26. Muraru D, Previtero M, Ochoa-Jimenez RC, et al. Prognostic validation of partition values for quantitative parameters to grade functional tricuspid regurgitation severity by conventional echocardiography. Eur Heart J Cardiovasc Imaging 2021;22:155-65.
27. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.
28. 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.
29. Lancellotti P, Pibarot P, Chambers J, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. Eur Heart J Cardiovasc Imaging 2022;23:e171-232.
30. Zaidi A, Oxborough D, Augustine DX, et al. Echocardiographic assessment of the tricuspid and pulmonary valves: a practical guideline from the British Society of Echocardiography. Echo Res Pract 2020;7:G95-122.
31. Badano LP, Hahn R, Rodríguez-Zanella H, et al. Morphological assessment of the tricuspid Apparatus and grading regurgitation severity in patients with functional tricuspid regurgitation. JACC Cardiovasc Imaging 2019;12:652-64.
32. Tomaselli M, Badano LP, Menè R, et al. Impact of correcting the 2D PISA method on the quantification of functional tricuspid regurgitation severity. Eur Heart J Cardiovasc Imaging 2022;23:1459-70.
33. Addetia K, Muraru D, Veronesi F, et al. 3-Dimensional echocardiographic analysis of the tricuspid annulus Provides new Insights into tricuspid valve geometry and dynamics. JACC Cardiovasc Imaging 2019;12:401-12.
34. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. J Am Soc Echocardiogr 2012;25:3-46.
35. Muraru D, Gavazzoni M, Heilbron F, et al. Reference ranges of tricuspid annulus geometry in healthy adults using a dedicated three-dimensional echocardiography software package. Front Cardiovasc Med 2022;9.
36. Badano LP, Kolias TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/industry task force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2018;19:591-600.
37. Badano LP, Muraru D, Parati G, et al. How to do right ventricular strain. Eur Heart J Cardiovasc Imaging 2020;21:825-7.
38. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513-21.
39. Morimont P, Lambermont B, Ghuysen A, et al. Effective arterial elastance as an index of pulmonary vascular load. Am J Physiol Heart Circ Physiol 2008;294:H2736-42.
40. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
41. Shrestha N. Detecting multicollinearity in regression analysis. Am J Appl Math Stat 2020;8:39-42.
42. Lee CY. Nested logistic regression models and ΔAUC applications: change-point analysis. Stat Methods Med Res 2021;30:1654-66.
43. 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;140:836-45.
44. Kammerlander AA, Marzluf BA, Graf A, et al. Right ventricular dysfunction, but not tricuspid regurgitation, is associated with outcome late after left heart valve procedure. J Am Coll Cardiol 2014;64:2633-42.

45. Gavazzoni M, Heilbron F, Badano LP, et al. The atrial secondary tricuspid regurgitation is associated to more favorable outcome than the ventricular phenotype. Front Cardiovasc Med 2022;9:1022755.
46. Topilsky Y, Khanna A, le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. Circ Cardiovasc Imaging 2012;5:314-23.
47. Praz F, Muraru D, Kreidel F, et al. Transcatheter treatment for tricuspid valve disease. EuroIntervention 2021;17:791-808.
48. 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.
49. 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.
50. Muraru D. 22nd annual Feigenbaum Lecture: right heart, right now: the role of three-dimensional echocardiography. J Am Soc Echocardiogr 2022;35:893-909.
51. 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.
52. Vanderpool RR, Pinsky MR, Naeije R, et al. RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. Heart 2015;101:37-43.
53. Kubba S, Davila CD, Forfia PR. Methods for evaluating right ventricular function and ventricular–arterial coupling. Prog Cardiovasc Dis 2016; 59:42-51.
54. Fortmeier V, Lachmann M, Körber MI, et al. Solving the pulmonary hypertension paradox in patients with severe tricuspid regurgitation by employing artificial intelligence. JACC Cardiovasc Interv 2022;15: 381-94.
55. Fei B, Fan T, Zhao L, et al. Impact of severe tricuspid regurgitation on accuracy of systolic pulmonary arterial pressure measured by Doppler echocardiography: analysis in an unselected patient population. Echocardiography 2017;34:1082-8.
56. Hsiao S-H, Lin S-K, Wang W-C, et al. Severe tricuspid regurgitation shows significant impact in the relationship among peak systolic tricuspid annular velocity, tricuspid annular plane systolic excursion, and right ventricular ejection fraction. J Am Soc Echocardiogr 2006; 19:902-10.
57. Tamborini G, Muratori M, Brusoni D, et al. Is right ventricular systolic function reduced after cardiac surgery? A two- and three-dimensional echocardiographic study. Eur J Echocardiogr 2009;10:630-4.
58. Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. Circ Res 1985;56:586-95.
59. Cohen-Solal A, Caviezel B, Himbert D, et al. Left ventricular-arterial coupling in systemic hypertension: analysis by means of arterial effective and left ventricular elastances. J Hypertens 1994;12:591-600.
60. Ikonomidis I, Aboyans V, Blacher J, et al. The role of ventricular-arterial coupling in cardiac disease and heart failure: assessment, clinical implications and therapeutic interventions. A consensus document of the European Society of Cardiology Working Group on Aorta & Peripheral Vascular Diseases, European Association of Cardiovascular Imaging, and Heart Failure Association. Eur J Heart Fail 2019;21:402-24.
61. Sanz J, García-Alvarez A, Fernández-Friera L, et al. Right ventriculo-arterial coupling in pulmonary hypertension: a magnetic resonance study. Heart 2012;98:238-43.
62. Brewis MJ, Bellofiore A, Vanderpool RR, et al. Imaging right ventricular function to predict outcome in pulmonary arterial hypertension. Int J Cardiol 2016;218:206-11.

Supplemental Table 1 Multivariate models using TAPSE/PASP, RV forward SV/ESV, and RVFWLS/PASP as continuous values in the same three models presented in Table 3 (models 1, 2, and 4, respectively)

Factor	HR (95% CI)	*P*
Model 1		
Severe TR (vs moderate)	3.43 (1.62-7.26)	<.01
Atrial fibrillation (yes vs no)	3.02 (1.33-6.91)	.01
Pulmonary arterial hypertension (yes vs no)	1.27 (0.97-1.65)	.07
3D RA maximum volume	0.99 (0.98-1.01)	.61
RV end-diastolic volume	1.00 (0.95-1.01)	.66
RVFWLS, %	0.96 (0.91-1.02)	.23
TAPSE/PASP	**0.07 (0.02-0.36)**	**<.01**
Model 2		
Severe TR (vs moderate)	3.45 (1.55-7.68)	<.01
Atrial fibrillation (yes vs no)	4.11 (1.76-9.60)	<.01
Pulmonary arterial hypertension (yes vs no)	1.30 (1.04-1.69)	.05
RV end-diastolic volume	1.00 (0.99-1.01)	.48
RVFWLS	0.97 (0.92-1.03)	.97
RV forward SV/ESV	**0.02 (0.02-0.28)**	**<.01**
Model 4		
Severe TR (vs moderate)	4.09 (1.89-8.89)	<.01
Atrial fibrillation (yes vs no)	3.05 (1.35-6.89)	<.01
Pulmonary arterial hypertension (yes vs no)	1.25 (0.97-1.63)	.09
RV end-diastolic volume	1.00 (0.99-1.01)	.74
RVFWLS	0.99 (0.92-1.09)	.95
RVFWLS/PASP	**0.10 (0.01-1.47)**	**.09**

ESV, end systolic volume; *PASP,* pulmonary arterial systolic pressure; *RV,* right ventricle; *SV,* stroke volume; *TAPSE,* tricuspid annular plane systolic excursion.

Supplemental Table 2 Univariate Cox regression analysis for correlates of the composite end point of all-cause death and hospitalization for HF

	Moderate TR (*n* = 107)		Severe TR (*n* = 73)	
Factor	HR (95% CI)	*P*	HR (95% CI)	*P*
TAPSE/PASP	0.01 (0.002-0.13)	<.01	0.43 (0.1-3.99)	.04
RVEF	0.15 (0.06-0.38)	<.01	0.67 (0.33-1.36)	.27
RVFWLS/PASP	0.02 (0.002-0.21)	<.001	0.22 (0.04-1.19)	.05
RV forward SV/ESV	0.10 (0.03-0.32)	<.001	0.15 (0.03-0.74)	.02

Supplemental Table 3 Correlates of RV forward SV/ESV

	Patients with RV forward SV/ESV ≥ 0.40 (*n* = 100)	Patients with RV forward SV/ESV < 0.40 (*n* = 80)	*P*
Clinical factors			
Age, y	72 ± 12	75 ± 15	.29
Gender, female	61 (60)	48 (60)	.36
NYHA functional class III or IV	30 (30)	45 (56)	.11
Body surface area, m^2	1.59 ± 0.58	1.48 ± 0.66	.28
Heart rate, beats/min	75 ± 16	78 ± 22	.32
Systolic blood pressure, mm Hg	132 ± 22	123 ± 20	.03
Diastolic blood pressure, mm Hg	75 ± 13	72 ± 12	.15
Diabetes	18 (18)	13 (15)	.37
Arterial hypertension	34 (34)	24 (30)	.42
Chronic obstructive pulmonary disease	12 (12)	10 (13)	.23
Ischemic heart disease	11 (11)	15 (19)	.13
Previous valve surgery	2 (2)	2 (3)	.61
Left heart characteristics			
LV ejection fraction, %	61 ± 7	60 ± 9	.47
Left atrial maximal volume, mL/m^2	48 ± 21	52 ± 22	.34
Elevated LV filling pressures	19 (19)	13 (16)	.41
TR severity			
Severe TR	27 (27)	45 (56)	<.001
2D vena contracta, cm	0.45 ± 0.22	0.76 ± 0.32	<.001
3D vena contracta area, cm^2	0.79 ± 0.57	1.17 ± 0.93	.03
EROA, cm^2	0.20 (0.10-0.24)	0.47 (0.31-0.65)	.002
EROA > 0.4 cm^2	11 (11)	31 (39)	<.001
Regurgitant fraction, %	22 ± 14	53 ± 15	<.001
TV remodeling			
Tenting height, mm	13.4 ± 4.7	14.7 ± 6.7	.31
Tenting volume, mL	3.3 ± 1.7	4.2 ± 1.76	.05
Tricuspid annular diameter, mm	39.8 ± 6.4	42.6 ± 7.3	.07
End-diastolic tricuspid annular area, cm^2	12.4 ± 3.3	13.4 ± 3.2	.11
End-systolic tricuspid annular area, cm^2	10.3 ± 3.2	11.2 ± .2	.23
Right atrium			
3D maximum volume, mL/m^2	53 ± 21	62 ± 37	.001
3D minimum volume, mL/m^2	42 ± 20	54 ± 25	.01
Estimated RA pressure, mm Hg	7 ± 3	6 ± 3	.34
Right ventricle			
End-diastolic basal diameter, mm/m^2	24 ± 3	26 ± 4	<.001
End-diastolic volume, mL/m^2	75 ± 23	100 ± 48	<.001
ESV, mL/m^2	40 ± 14	64 ± 40	<.001
SV, mL/m^2	36 ± 12	37 ± 14	.51
TAPSE, mm	20 ± 5	17 ± 5	.001
Free wall S′ velocity, cm/sec	12 ± 3	10 ± 3	.001
RVFWLS, −%	20 ± 5	17 ± 4	.001
Four-chamber strain, −%	16 ± 4	14 ± 5	.001
RVEF, %	48 ± 8	40 ± 10	<.001
PASP, mm Hg	42 ± 15	56 ± 25	<.001

(*Continued*)

Supplemental Table 3 (*Continued*)

	Patients with RV forward SV/ESV ≥ 0.40 (*n* = 100)	Patients with RV forward SV/ESV < 0.40 (*n* = 80)	*P*
RV-PA coupling			
TAPSE/PASP, mm/mm Hg	0.54 ± 0.24	0.36 ± 0.21	.02
RVEF/PASP, %/mm Hg	1.30 ± 0.51	0.89 ± 0.45	<.001
RVFWLS/PASP, (−%)/mm Hg	0.52 ± 0.22	0.38 ± 0.22	<.001
RV forward SV/ESV	0.70 ± 0.22	0.23 ± 0.10	<.001
Events			
Combined death and HF hospitalizations	14 (14)	58 (73)	<.001
Death	7 (7)	21 (26)	.001
HF hospitalizations	12 (12)	52 (65)	<.001

2D, Two-dimensional; *LV*, left ventricular; *NYHA*, New York Heart Association.
Data are expressed as mean ± SD, number (percentage), or median (interquartile range).

Supplemental Table 4 Reproducibility of RV and tricuspid RegVol measurement

	First measurement	Intraobserver		Interobserver	
	CV	ICC	CV	ICC	CV
RV end-diastolic volume	0.26	0.995	0.26	0.973	0.23
RV ESV	0.28	0.980	0.29	0.980	0.28
RegVol	0.15	0.975	0.15	0.955	0.13
RV forward SV/ESV	0.14	0.961	0.12	0.943	0.11

CV, Coefficient of variation; *ICC*, intraclass correlation coefficient.