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ORIGINAL RESEARCH

Right Heart Remodeling Redefines Risk in Significant Secondary Tricuspid Regurgitation Without Indication for Intervention

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BACKGROUND: The prognostic significance of right heart remodeling (RHR) in patients with secondary tricuspid regurgitation (STR) who do not meet guideline-based indications for tricuspid valve surgery remains uncertain. We evaluated whether advanced markers of RHR are associated with outcomes in medically managed patients with significant STR.

METHODS: We retrospectively included 755 patients with significant STR (age 75±12 years). Patients were stratified into 3 groups: Group 1, no current surgical indication (n=519); Group 2, meeting Class I/IIa guideline criteria (n=144); and Group 3, deemed inoperable (n=92). RHR markers included right atrial volume index, right ventricular end-diastolic volume index, forward stroke volume/right ventricular end-systolic volume ratio, and effective right ventricular ejection fraction. The primary end point was a composite of all-cause mortality or heart failure hospitalization.

RESULTS: Group 1 patients had less severe STR and less advanced right ventricular remodeling than Groups 2 and 3. Over a median follow-up of 24 months (interquartile range, 11–34), 330 primary events occurred; 64 patients underwent tricuspid valve intervention. In Group 1, 30-month event-free survival was 71±4% with no RHR markers, 65±3% with 1 or 2 markers, and 33±9% with ≥3 markers (adjusted hazard ratio [aHR], 2.76 [95% CI, 1.74–4.37]; *P*<0.001). Patients in Group 1 with ≥3 RHR markers had event rates comparable to Group 2 (aHR, 2.79 [95% CI, 1.94–4.02]; *P*<0.001) and Group 3 (aHR, 4.08 [95% CI, 2.73–6.09]; *P*<0.001).

CONCLUSIONS: Among patients with significant STR without surgical indications, ≥3 markers of RHR identify a high-risk phenotype with outcomes similar to those meeting surgical criteria or considered inoperable.

Key Words: guidelines ■ outcomes ■ right heart remodeling ■ secondary tricuspid regurgitation

Significant secondary tricuspid regurgitation (STR) is a progressive condition associated with substantial morbidity, impaired quality of life, and increased risks of mortality.[1,2] Current American College of Cardiology/American Heart AssociationACC/AHA and European Society of Cardiology/European Association for Cardio-Thoracic Surgery valvular heart disease guidelines recommend tricuspid valve (TV)

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with significant secondary tricuspid regurgitation without guideline-based indications for intervention, the presence of ≥3 advanced echocardiographic right heart remodeling markers identifies a high-risk phenotype with outcomes comparable to those meeting surgical criteria or deemed inoperable.

What Are the Clinical Implications?

- Comprehensive right heart remodeling assessment may refine risk stratification and support closer surveillance in patients with significant secondary tricuspid regurgitation who do not yet meet formal guideline criteria for intervention.
- Multicenter prospective and randomized studies are needed to determine whether incorporation of these parameters into clinical decision-making could identify candidates for earlier surgical intervention.

Nonstandard Abbreviations and Acronyms

EDV	end-diastolic volume
ESV	end-systolic volume
MR	mitral regurgitation
RHR	right heart remodeling
STR	secondary tricuspid regurgitation
TV	tricuspid valve

intervention in symptomatic patients with severe STR or in asymptomatic patients with severe STR and right ventricular (RV) dilatation, provided that severe RV or left ventricular (LV) dysfunction and pulmonary hypertension are absent (Class I/IIa).[3,4] However, these recommendations are primarily based on expert consensus and limited observational data. Their applicability is further constrained by the limited accuracy of conventional echocardiographic parameters in assessing STR severity and right heart remodeling (RHR), which do not adequately reflect the complex pathophysiology and natural history of the disease.[3–5] Historically, the high in-hospital mortality associated with isolated TV surgery (~9%–10%) has contributed to significant therapeutic inertia and undertreatment.[6,7] Recent observational studies have suggested that earlier surgical intervention in asymptomatic patients with significant STR may reduce in-hospital mortality, improve midterm survival, decrease heart failure hospitalizations, and enhance functional capacity.[8–10] These findings support a paradigm shift toward earlier intervention, before the onset of advanced RHR, as a means of improving long-term outcomes.[8–11]

Advances in echocardiography have recently enabled a more comprehensive characterization of STR-induced remodeling of the right atrium (RA)[12] and RV,[13,14] as well as RV–pulmonary artery (PA) coupling,[15] providing incremental prognostic information beyond conventional measures.[5] Nonetheless, in patients with moderate or severe STR who do not meet current guideline criteria for TV intervention, the prevalence and prognostic significance of these advanced markers of RHR remain uncertain.

Accordingly, the present study aimed to evaluate the association between advanced echocardiographic markers of RHR and clinical outcomes in patients with significant STR without guideline-based indications for TV intervention.

METHODS

Transparency and Openness Promotion Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We reanalyzed prospectively collected echocardiographic data from consecutive euvolemic outpatients with moderate or severe STR between September 2019 and July 2024 at 2 tertiary referral centers: San Luca Hospital, Istituto Auxologico Italiano, IRCCS (Milan, Italy), and Yonsei University College of Medicine (Seoul, South Korea). Patients with primary TR, cardiac implantable electronic device-related TR, previous surgical or transcatheter TV interventions, inadequate echocardiographic image quality, life expectancy <1 year, and follow-up shorter than 6 months were excluded. The study was approved by the ethics committee of the Istituto Auxologico Italiano, IRCCS (record #2021_05_18_13, approved on May 18, 2021) and conducted in accordance with the Declaration of Helsinki. Owing to the retrospective design of the study and the use of anonymized data, the Ethics Committee waived the need for informed consent.

Baseline demographic characteristics, comorbidities, and New York Heart Association functional class were obtained from electronic medical records. Symptomatic status was determined during outpatient visits by multidisciplinary heart valve teams through detailed clinical interviews and physical examination. In patients with uncertain symptom status, results from exercise testing performed within 12 weeks of

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the baseline echocardiography were also considered. Potential sources of bias were mitigated by consecutive patient inclusion, blinded echocardiographic analysis, and standardized data collection across centers.

Echocardiography

All patients underwent comprehensive 2- and 3-dimensional echocardiography using commercially available systems (Vivid E9/E95; GE Healthcare, Horten, Norway) equipped with 4V/4Vc probes. Image analysis was performed offline using EchoPAC version 204 (GE Healthcare) by certified researchers with dedicated expertise in advanced echocardiographic assessment, including comprehensive right heart quantification. All readers were blinded to clinical data and outcomes at the time of analysis. Conventional echocardiographic parameters, including PA systolic pressure (PASP), left and RA, RV, and LV, and left-sided valvular disease severity were assessed according to current recommendations.[3,4,16,17]

RA volume was measured from an RV-focused apical view.[12,18] RV systolic function was assessed using tricuspid annular plane systolic excursion, RV ejection fraction (RVEF) calculated using the RV end-diastolic (EDV) and RV end-systolic (ESV) volumes measured with 4DAutoRVQ, effective RVEF (eRVEF), calculated as RV forward stroke volume (fSV) divided by RV EDV.[14] RV–PA coupling was evaluated as the fSV/RV ESV ratio.[15] The use of 3-dimensional echocardiography to measure RVSV has recently been validated against an invasive reference.[19] The reproducibility of eRVEF and forward SV/ESV has been previously validated in dedicated methodological studies from our group demonstrating excellent intra- and interobserver agreement[14,15]; therefore, a separate reproducibility analysis was not repeated in the present outcome-focused investigation. The tricuspid annulus diameter was measured in the standard apical 4-chamber view at end-diastole.[20] STR effective regurgitant orifice area and regurgitant volume were quantified using the corrected Proximal Isovelocity Surface Area. method,[21–23] and overall STR severity was graded according to the recently proposed 5-grade scheme.[24] STR phenotypes (atrial versus ventricular) were classified following contemporary recommendations.[24,25] Ventricular STR was further classified into left-sided cardiac disease, pulmonary hypertension, and RV dysfunction.[26]

Definition of Groups and Study End Point

Patients were hierarchically categorized into 3 groups: Group 1, patients with moderate or severe STR who did not meet current guideline-based indications for intervention; Group 2, patients fulfilling American College of Cardiology/American Heart Association and European Society of Cardiology/European Association for Cardio-Thoracic Surgery Class I/IIa recommendations for TV intervention,[3,4] including (1) symptomatic patients with severe STR, (2) asymptomatic patients with severe STR and RV dilatation (RV EDV indexed [RV EDVi] >95 mL/m^2), or (3) candidates for left-sided valvular surgery with concomitant moderate-to-severe STR[4]; and Group 3, patients with severe STR considered inoperable, defined by LVEF <30%, RVEF <35%, or PASP ≥50 mm Hg.[4]

Group 1 patients were further stratified according to the number of echocardiographic markers of RHR: RA volume indexed (RAVi) >47 mL/m^2, RV EDVi >95 mL/m^2, fSV/RV ESV <0.40, and eRVEF <20%. These thresholds were selected based on prior studies linking them to adverse outcomes.[12,14,15] Patients were classified as having 0, 1-2, or 3-4 markers.

The primary endpoint was a composite of all-cause mortality or heart failure hospitalizations.[24] Survival and hospitalization data were obtained via structured patient interviews and review of clinical records every 6 months. Follow-up was censored at the first occurrence of the composite endpoint, TV intervention, or the last available follow-up in event-free patients. All clinical events were independently adjudicated by physicians blinded to imaging and clinical data.

Statistical Analysis

The distribution of continuous quantitative variables was assessed by the Shapiro–Wilk test. Continuous variables are presented as mean±SD or median (interquartile range) depending on their distribution. Differences among groups were assessed using 1-way ANOVA for normally distributed variables or the Kruskal–Wallis test for nonnormally distributed variables. When overall differences were significant, post hoc pairwise comparisons were performed using the Bonferroni correction. Categorical variables were presented as counts and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. To assess potential multicollinearity among echocardiographic markers of right heart remodeling, we calculated variance inflation factors. Kaplan–Meier curves were used to estimate event-free survival, and 95% confidence bands were displayed using Greenwood's formula. Adjusted survival curves were generated using inverse probability of treatment weighting derived from a multinomial propensity score model that included age, sex, chronic kidney disease, atrial fibrillation, and ischemic heart disease. These variables were chosen based on their established association with adverse outcomes in STR, and to account for potential confounding. Hazard ratios (HRs) and 95% CIs were estimated using weighted Cox proportional hazards models with robust variance estimation. Global *P* values were derived

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Table Demographics and Baseline Characteristics of the Study Population

	All (n=755)	Group 1 (n=519)	Group 2 (n=144)	Group 3 (n=92)	*P* value*
Clinical characteristics					
Age, y	75±12	75±11‡	76±13‡	70±15	<0.001§
Sex, male, n (%)	340 (45)	220 (42)‡	66 (46)‡	54 (59)	0.015§
Body surface area, m^2	1.75±0.22	1.75±0.22	1.75±0.23	1.76±0.23	0.898
New York Heart Association class III–IV, n (%)	244 (32)	0 (0)†‡	94 (65)‡	67 (73)	<0.001§
Hypertension, n (%)	568 (75)	392 (76)	107 (74)	69 (75)	0.954
Diabetes, n (%)	186 (25)	113 (22)‡	34 (24)‡	39 (42)	<0.001§
Chronic obstructive pulmonary disease, n (%)	196 (26)	149 (29)‡	32 (22)	15 (16)	0.023§
Coronary artery disease, n (%)	123 (16)	87 (17)	17 (12)	19 (21)	0.174
Left heart surgery, n (%)	103 (14)	61 (12)‡	21 (15)	21 (23)	0.016§
Chronic kidney disease (glomerular filtration rate <30 mL/min), n (%)	157 (21)	84 (16)†‡	46 (32)	27 (29)	<0.001§
Atrial fibrillation, n (%)	519 (69)	343 (66)	109 (76)	67 (73)	0.059
Loop diuretics ≥125 mg, n (%)	43 (6)	5 (1)†‡	21 (14)	17 (15)	<0.001§
Ventricular TR, n (%)	419 (56)	248 (56)†‡	91 (63)‡	80 (87)	<0.001§
Tricuspid valve interventions, n (%)	64 (9)	14 (3)†‡	38 (26)‡	12 (13)	<0.001§
Echocardiographic parameters					
Left ventricular ejection fraction, %	53±14	54±13‡	52±15	49±18	0.001§
Left atrial volume indexed, mL/m^2	59 (47–76)	58 (47–73)‡	61 (48–78)‡	72 (54–100)	<0.001§
TR effective regurgitant orifice area, cm^2	0.40 (0.28–0.57)	0.33 (0.25–0.42)†‡	0.66 (0.48–0.98)	0.65 (0.56–0.82)	<0.001§
TR regurgitant volume, mL	39±22	31±11†‡	55±24‡	64±27	<0.001§
Pulmonary artery systolic pressure, mm Hg	44±17	43±16‡	40±12‡	58±19	<0.001§
RV end-diastolic volume indexed, mL/m^2	95±38	82±26†‡	114±43‡	137±45	<0.001§
RV end-systolic volume indexed, mL/m^2	48±27	40±20†‡	58±27‡	78±31	<0.001§
RV ejection fraction, %	51±10	53±10†‡	50±9‡	44±10	<0.001§
Effective RV ejection fraction, %	28±10	31±10†‡	23±8‡	20±7	<0.001§
Tricuspid annular plane systolic excursion, mm	18±5	18±5	17±5	17±5	0.256
Forward stroke volume/ end-systolic volume	0.56 (0.35–0.79)	0.64 (0.45–0.93)†‡	0.43 (0.29–0.59)‡	0.29 (0.19–0.43)	<0.001§
Tricuspid annulus 4-chamber, mm	40±7	38±6†‡	43±7	44±7	<0.001§
Right atrial volume indexed, mL/m^2	55 (40–79)	50 (37–68)†‡	72 (50–108)‡	81 (60–139)	<0.001§
Mitral regurgitation, n (%)					<0.001§
0–1	475 (63)	339 (65)†‡	80 (55)	56 (61)	
2–3	280 (37)	180 (35)	64 (45)	36 (39)	
Mitral stenosis, n (%)					0.444
0–1	743 (98)	513 (99)	141 (98)	89 (97)	
2–3	12 (2)	6 (1)	3 (2)	3 (3)	
Aortic regurgitation, n (%)					0.186
0–1	693 (92)	474 (91)	135 (94)	84 (91)	
2–3	62 (8)	45 (9)	9 (6)	8 (9)	
Aortic stenosis, n (%)					0.006§
0–1	707 (94)	495 (95)†‡	127 (88)	85 (92)	
2–3	48 (6)	24 (5)	17 (12)	7 (8)	
TR severity, n (%)					<0.001§
2	397 (52)	373 (72)†‡	24 (17)†	0 (0)	
3	209 (28)	122 (23)†‡	40 (28)	47 (51)	
4	82 (11)	20 (4)†‡	35 (24)	27 (29)	
5	67 (9)	4 (1)†‡	35 (31)	18 (20)	

Values: mean (95% CI), median (interquartile range) or n (%).
RV indicates right ventricular; and TR, tricuspid regurgitation.
**P* values show differences between groups.
†*P*<0.05 vs Group 2.
‡*P*<0.05 vs Group 3.
§Indicates *P*<0.05.

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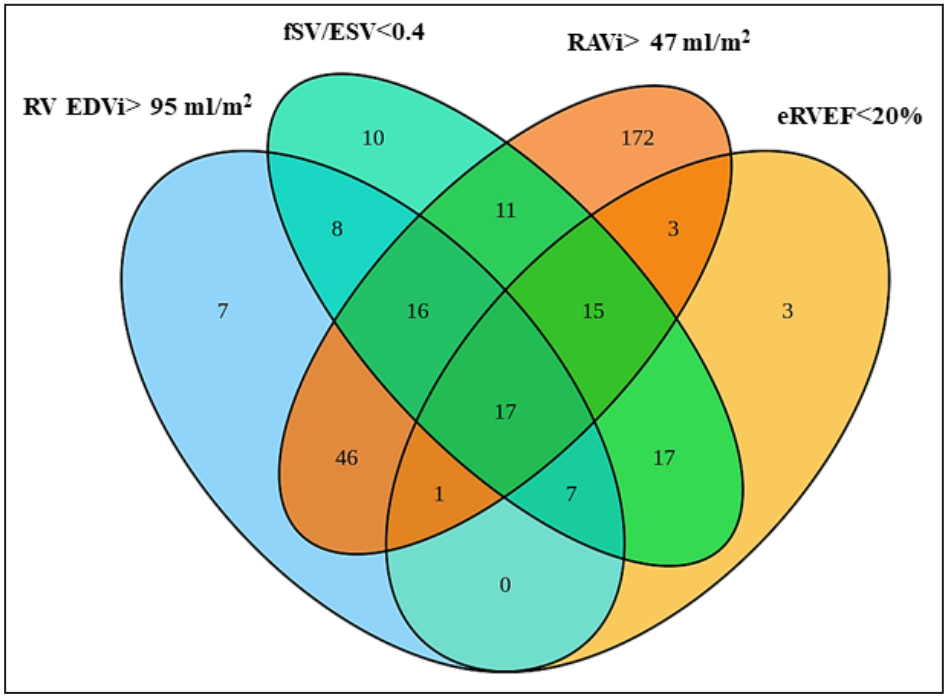

Figure 1. Overlap of echocardiographic markers of right heart remodeling.
Venn diagram illustrating the distribution and overlap of right heart dysfunction markers among asymptomatic patients with moderate or severe STR. eRVEF indicates effective right ventricular ejection fraction; fSV/ESV, forward stroke volume to end-systolic volume; RAVi, right atrial volume index; and RV EDVi, right ventricular end-diastolic volume index.

from robust Wald tests based on the Cox models; therefore, they reflect model-based comparisons and may not directly correspond to visual differences observed in the unadjusted Kaplan–Meier curves. The proportional hazards assumption was assessed. To evaluate the impact of markers of right heart dysfunction and Class I/IIa guideline recommendations on the composite endpoint under medical management, multivariable Cox regression models were used. To address potential between-center heterogeneity, sensitivity analyses were performed using alternative approaches: (1) including the study center as a covariate (fixed effect), and (2) stratifying Cox models by center. These approaches were applied separately and not simultaneously. No formal sample size calculation was performed due to the observational design. Statistical analyses were performed using R (version 4.3.2; R Foundation for Statistical Computing), with a 2-sided significance level of $P<0.05$ considered significant.

RESULTS

Baseline Characteristics

After applying exclusion criteria, 755 patients were included in the final cohort (mean age 75±12 years, 55% women, 48% severe STR; Figures S1–S21). Of these, 519 patients had moderate or severe STR without indications for TV intervention (Group 1), 144 fulfilled Class I/IIa guideline criteria for surgical intervention (Group 2), and 92 patients were considered inoperable (Group 3).

Group 1 patients were older and more frequently male than those in Groups 2 and 3. They also required lower doses of loop diuretics, and had lower prevalence of prior left-sided valve interventions, advanced chronic kidney disease, and ventricular STR. Group 1 patients showed higher LVEF, RVEF, eRVEF, and RV–PA coupling (fSV/ESV), smaller RV and RA volumes, higher PASP, and smaller STR effective regurgitant orifice area and regurgitant volume (Table). The distribution of STR phenotypes differed significantly across study groups (χ^2=90.3, degrees of freedom=6; $P<0.001$), with atrial STR predominating in Group 1 and pulmonary hypertension more frequently observed in Group 3 (Figure S2).

Among Group 1 patients, RAVi >47 mL/m^2 was present in 288 patients (86.5%), RVEDVi >95 mL/m^2 in 85 (25.5%), fSV/ESV <0.40 in 53 (15.9%), and eRVEF <20% in 41 (12.3%). The most frequent isolated abnormality was RA enlargement (RAVi >47 mL/m^2, 172 patients, 51.7%), whereas isolated RV–PA uncoupling (fSV/ESV <0.40), RV dilatation (RVEDVi >95 mL/m^2), and RV dysfunction (eRVEF <20%) were observed in 10 (3.0%), 7 (2.0%), and 3 patients (0.9%), respectively.

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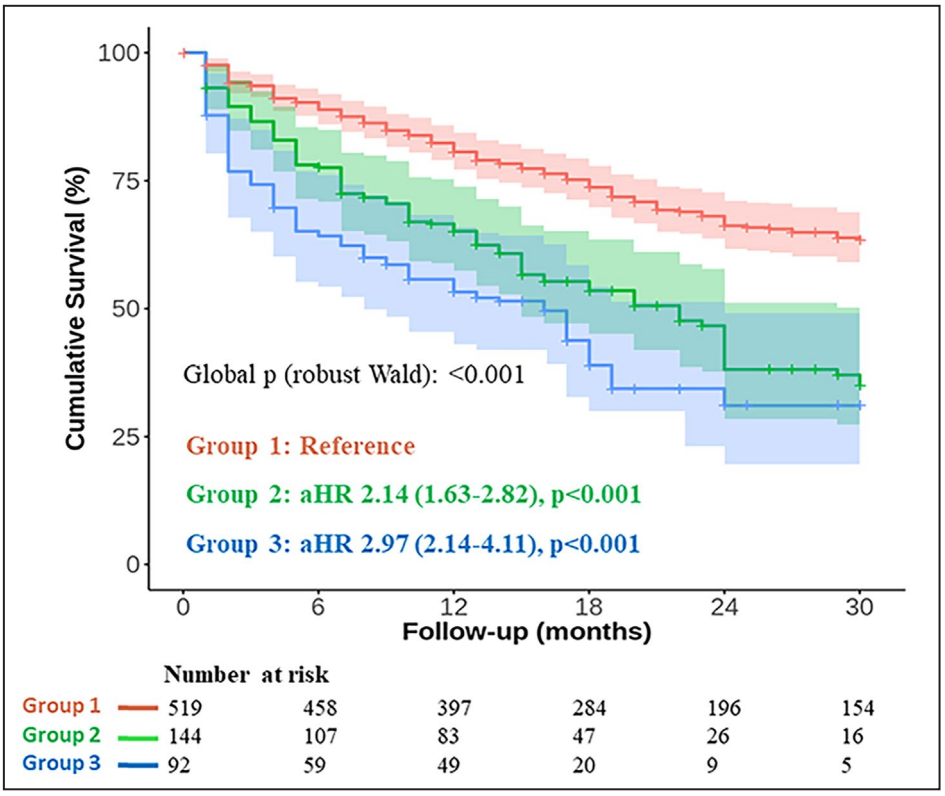

Figure 2. Kaplan–Meier curves for the composite end point of all-cause mortality or heart failure hospitalization in patients with moderate or severe STR, stratified by guideline-derived clinical groups.

P value derived from inverse probability weighted Cox regression with robust variance estimation. The numbers in brackets refer to the 95% CI for each aHR. aHR indicates adjusted hazard ratio; and STR, secondary tricuspid regurgitation.

Seventeen patients (5.1%) exhibited all 4 RHR markers simultaneously, and 16 patients (4.8%) had the triple combination of RVEDVi >95 mL/m^2, fSV/ESV <0.40, and RAVi >47 mL/m^2. Two-marker overlaps were also frequent, most notably RVEDVi >95 mL/m^2 combined with RAVi >47 mL/m^2 (46 patients, 13.8%, Figure 1).

Survival Analysis

Over a median follow-up of 24 months (interquartile range, 11–34 months), 330 patients experienced the composite end point (196 heart failure hospitalizations, 187 deaths). During follow-up, 64 patients underwent TV intervention (10 surgical annuloplasties, 54 transcatheter edge-to-edge repairs) with Group 1 demonstrating a significantly lower rate of TV interventions than Groups 2 and 3 (*P*<0.001; Table).

At 30 months, event-free survival differed significantly across groups, being lowest in inoperable patients (Group 3), intermediate in those meeting Class I/IIa criteria for TV intervention (Group 2), and highest in patients without intervention criteria (Group 1) (31±7%, 35±6%, and 63±2%, respectively; global robust Wald *P*<0.001 from the weighted Cox model; Figure 2). Group 3 had an almost 3-fold higher risk of adverse events versus Group 1 (adjusted HR [aHR], 2.97 [95% CI, 2.14–4.11]; *P*<0.001), and Group 2 had an ~2-fold higher risk (aHR, 2.14 [95% CI, 1.63–2.82]; *P*<0.001).

Stratification of Group 1 by RHR markers revealed a stepwise gradient in risk (Figure 3). Event-free survival at 30 months was 71±4% in patients without RHR markers, 65±3% with 1 to 2 markers (aHR, 1.27 [95% CI, 0.89–1.82]; *P*=0.24), and 33±9% with ≥3 markers (aHR, 2.76 [95% CI, 1.74–4.37]; *P*<0.001). Outcomes in Group 2 (aHR, 2.79 [95% CI, 1.94–4.02]) and Group 3 (aHR, 4.08 [95% CI, 2.73–6.09]; *P*<0.001) were worse compared with Group 1 patients without RHR markers. Using Group 1 with 3 to 4 markers as reference, outcomes were similar to guideline-eligible patients in Group 2 (aHR, 0.88 [95% CI, 0.59–1.32]; *P*=0.53) and inoperable patients in Group 3 (aHR, 1.06 [95% CI, 0.69–1.64]; *P*=0.78).

Including the study center as a covariate did not improve model fit (*P*=0.25). In sensitivity analyses, stratification by center yielded similar HRs estimates with a C-statistic of 0.71, suggesting no meaningful heterogeneity across centers.

After exclusion of patients with severe left-sided valvular heart disease (n=104), event-free survival

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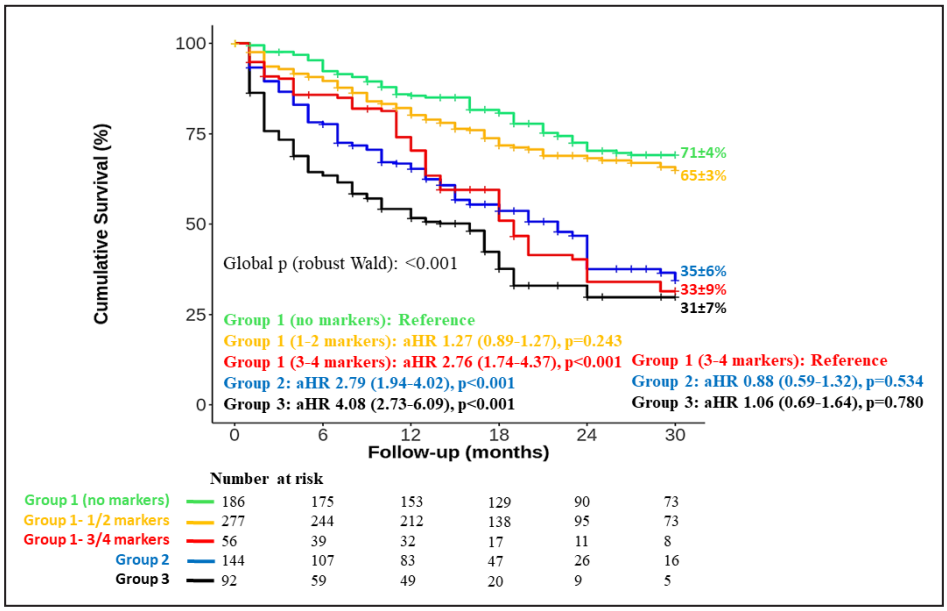

Figure 3. Cumulative survival in moderate or severe secondary tricuspid regurgitation by clinical groups and right heart dysfunction markers.
P value derived from inverse probability weighted Cox regression with robust variance estimation. The numbers in brackets refer to the 95% CI for each aHR. aHR indicates adjusted hazard ratio.

curves remained similar across groups (Figure 4A and 4B).

Within Group 1, multivariable adjustment for age, sex, chronic kidney disease, atrial fibrillation, and ischemic heart disease demonstrated that all 4 RHR markers were independently associated with the composite end point when analyzed as continuous variables: larger RAVi (aHR, 1.07 per 10 mL/m^2 increase [95% CI, 1.01–1.12]; *P*=0.013), larger RVEDVi (aHR, 1.08 per 10 mL/m^2 increase [95% CI, 1.02–1.14]; *P*=0.014), lower fSV/ESV ratio (aHR, 1.13 per 0.1 unit decrease [95% CI, 1.02–1.25]; *P*=0.021), and reduced eRVEF (aHR, 1.51 per 5% decrease [95% CI, 1.25–1.83]; *P*<0.001) (Figure 5). No evidence of collinearity was detected among these variables.

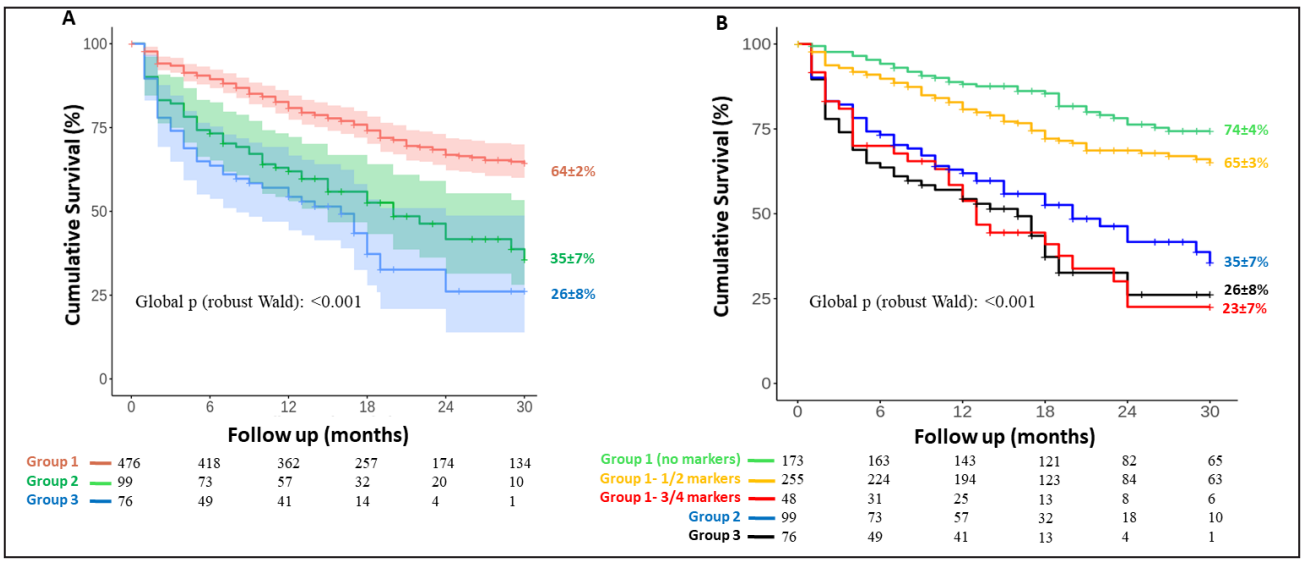

Figure 4. Kaplan–Meier curves for the composite end point of all-cause mortality or heart failure hospitalization in patients with significant secondary tricuspid regurgitation after exclusion of severe left-sided valvular heart disease.
A, Event-free survival stratified by guideline-derived clinical groups. **B**, Event-free survival in Group 1 stratified by right heart remodeling markers. *P* value derived from inverse probability weighted Cox regression with robust variance estimation.

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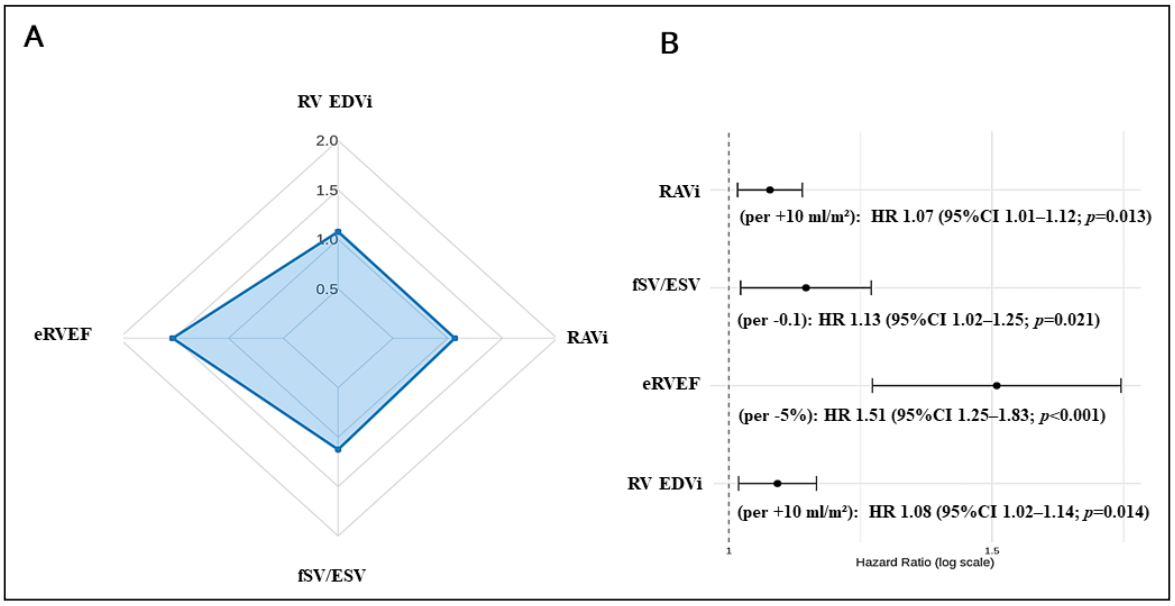

Figure 5. Advanced echocardiographic markers of right heart remodeling and risk of adverse outcomes in secondary tricuspid regurgitation.
A, Radar plot illustrating the relative magnitude of advanced right heart remodeling parameters, including RV EDVi, RAVi, fSV/ESV, and eRVEF. **B**, Forest plot displaying the association between each remodeling parameter and the composite end point of all-cause mortality or heart failure hospitalization. HRs are plotted on a logarithmic scale. eRVEF indicates effective right ventricular ejection fraction; fSV/ESV, forward stroke volume to end-systolic volume; HR, hazard ratio; RAVi, right atrial volume index; and RV EDVi, right ventricular end-diastolic volume index.

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DISCUSSION

In this multicenter cohort of consecutive patients with moderate or severe STR, stratified according to current guideline criteria for TV intervention,[3,4] our study demonstrates the prognostic significance of advanced echocardiographic markers of RHR. The main findings are (1) after multivariable adjustment, the incidence of the composite end point of all-cause mortality or heart failure hospitalizations increased progressively from patients with STR without guideline-based indications for TV intervention (Group 1) to those meeting Class I/IIa guideline criteria (Group 2) and inoperable patients (Group 1); (2) within Group 1, the risk of adverse outcomes increased with the number of echocardiographic markers of RHR; and (3) Group 1 patients presenting with 3 to 4 markers exhibited survival outcomes comparable to those of guideline-eligible and inoperable patients.

Incremental Value of Advanced Echocardiography in STR

Echocardiography remains the cornerstone for assessing right heart structure and function in STR; however, conventional parameters of RV function are limited by geometric complexity and load dependency, which may reduce sensitivity for detecting early maladaptive remodeling.[5,20,24] Consequently, the hemodynamic burden of TR may be underestimated, delaying recognition of optimal timing for TV intervention as recommended by current guidelines.[3,4]

Recent evidence indicates that advanced echocardiographic indices provide incremental prognostic information by capturing the functional adaptation of the right heart to STR.[12–15] RA and RV volumes, in particular, are robust metrics of chamber remodeling that correlate strongly with cardiac magnetic resonance measurements,[5,20] and they refine both pathogenetic[25,27] and risk stratification,[12,13] identifying thresholds that may guide intervention timing (eg, RVEDVi >95 mL/m^2).[4,24] The fSV/ESV ratio serves as a noninvasive index of RV–PA coupling, circumventing the need for Doppler PASP estimation and demonstrating stronger associations with outcomes than the traditional tricuspid annular plane systolic excursion/PASP.[15] eRVEF, which accounts for regurgitant volume, overcomes load dependence of conventional RVEF and provides additional prognostic information.[14]

In our cohort, each of these advanced echocardiographic parameters was independently associated with adverse outcomes after multivariable adjustment. eRVEF and fSV/ESV showed the strongest associations, followed by RVEDVi and RAVi, delineating a continuum of RHR culminating in advanced RV dysfunction.[28] Notably, this study is the first to quantify

the graded risk conferred by multiple RHR markers. Among asymptomatic patients without guideline-based intervention criteria, 53% exhibited 1 to 2 markers, and 11% demonstrated ≥3 markers, highlighting a substantial subset of patients with early maladaptive remodeling who may benefit from earlier referral and intervention.

Clinical Implications

These findings support the integration of advanced right heart parameters into routine echocardiographic evaluation of STR. Parameters such as eRVEF and fSV/ESV may serve as robust markers of maladaptive RHR, enabling timely referral to specialized valve centers, optimal intervention, and potentially improved outcomes.[24] Prospective multicenter studies are warranted to validate these indices as objective triggers for intervention and to inform future risk-stratification algorithms and guideline recommendations.

Limitations

This study has several limitations. First, its retrospective design and inclusion of patients with high-quality imaging may introduce selection bias. In addition, systematic longitudinal assessment of symptom progression and echocardiographic remodeling was not available; therefore, we could not determine whether patients in Group 1 developed symptoms, experienced worsening of right heart parameters, or progressed to meet guideline-based criteria for intervention during follow-up. The low TV intervention rate reflects the persistent undertreatment of STR in contemporary practice, despite increasing intervention rates over time.[11] The limited number of treated patients, together with nonrandomized treatment allocation, precluded meaningful comparisons between interventional and medical management strategies. Second, cause-specific mortality was not adjudicated; however, the use of all-cause mortality aligns with TVARC recommendations.[24] Third, thresholds for RHR markers were derived from retrospective observational studies and have not yet been validated in large-scale populations.[12–15] Fourth, the absence of an independent validation cohort precluded external confirmation. Finally, incomplete biomarker data limited the evaluation of BNP's prognostic impact.

CONCLUSIONS

In a multicenter cohort of patients with moderate or severe STR, advanced quantitative echocardiographic markers of RHR provided robust prognostic information beyond current guideline criteria. Patients with multiple RHR markers experienced outcomes comparable to guideline-eligible or inoperable patients. These results support a paradigm shift toward earlier detection and risk stratification using advanced echocardiographic parameters to improve clinical outcomes in patients with significant STR.

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ARTICLE INFORMATION

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Supplemental Material

Figures S1–S21
STROBE Checklist

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