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ORIGINAL PAPER

Sex-specific differences in right heart remodelling and patient outcomes in secondary tricuspid regurgitation

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Aims Current guidelines lack sex-specific thresholds for assessing secondary tricuspid regurgitation (STR) severity and right ventricular (RV) and tricuspid annulus (TA) remodelling. We aimed to determine whether risk-based cut-offs for these parameters differ between men and women with STR.

Methods and results We included 554 patients (74 ± 13 years, 51% women) with moderate or severe STR. The primary endpoint was all-cause mortality or heart failure hospitalization. Women were older ($P < 0.001$) and had a higher prevalence of atrial fibrillation ($P = 0.008$) and atrial STR ($P < 0.001$), whereas men more frequently had coronary artery disease ($P < 0.001$), chronic kidney disease ($P = 0.005$), and mitral regurgitation ($P < 0.001$). Women exhibited smaller RV and TA dimensions and higher RV ejection fraction (RVEF) ($P < 0.001$). Over a median follow-up of 19 (8–27) months, 230 patients reached the composite endpoint. Event-free survival at 2 years was comparable between sexes ($P = 0.183$), even after inverse propensity weighting ($P = 0.342$). Sex-specific thresholds for STR severity were lower in women for effective regurgitant orifice area (EROA) (0.36 cm^2 vs. 0.43 cm^2) and regurgitant volume (RegVol) (31 mL vs. 35 mL) but higher for regurgitant fraction (46% vs. 39%). Women also exhibited comparable risk at lower RV end-diastolic (81 mL/m^2 vs. 96 mL/m^2) and end-systolic volumes (37 mL/m^2 vs. 49 mL/m^2), higher RVEF (49% vs. 41%), and smaller TA diameter (19 mm/m^2 vs. 22 mm/m^2).

Conclusion In STR, women face a similar risk at lower EROAs and RegVols, along with smaller RV volumes, higher RVEF, and reduced TA dimensions. These findings highlight the importance of incorporating sex-specific thresholds into clinical decision-making when assessing STR severity and right heart remodelling.

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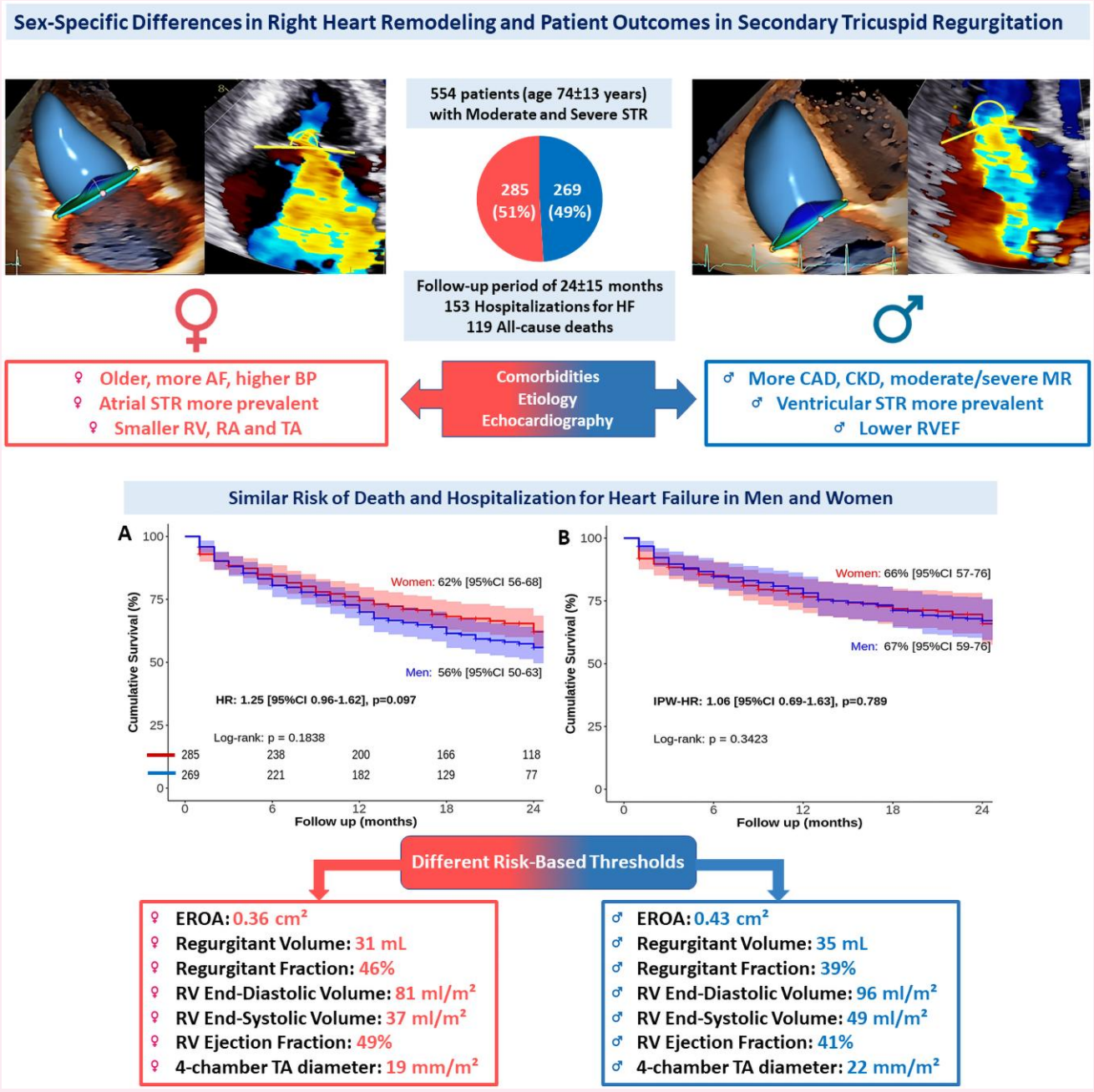
Graphical Abstract



Sex-specific differences in right heart remodelling and outcomes in secondary tricuspid regurgitation. While overall survival rates were similar, men and women differed in comorbidities and risk-based thresholds for STR severity, RV remodelling, and TA dilation. (*A*) Kaplan–Meier curves comparing cumulative survival between women (red) and men (blue). (*B*) Kaplan–Meier curves adjusted using inverse probability weighting. AF, atrial fibrillation; BP, blood pressure; EROA, effective regurgitant orifice area; HF, heart failure; HR, hazard ratio; IPW-HR, inverse probability weighted hazard ratio; RA, right atrium; RV, right ventricle; RVEF, right ventricular ejection fraction; STR, secondary tricuspid regurgitation; TA, tricuspid annulus.

Keywords secondary tricuspid regurgitation • echocardiography • sex differences • right ventricle • tricuspid annulus • outcome

Introduction

Recent studies have revealed significant sex differences among patients with secondary tricuspid regurgitation (STR), including variations in prevalence, underlying aetiology, associated comorbidities, and outcomes.[1–3] The Tricuspid Valve Academic Research Consortium (TVARC) recently published a state-of-the-art review that standardized the definition of right heart remodelling in patients with tricuspid regurgitation (TR).[4] However, neither the current guidelines[5,6] nor the TVARC[4] framework offers sex-specific thresholds for grading STR severity or evaluating right ventricular (RV) and tricuspid annulus (TA) remodelling in patients with significant STR.

Accordingly, our study aimed to (i) compare the outcomes between women and men with moderate and severe STR under medical treatment, (ii) evaluate whether the parameters of right heart remodelling associated with adverse events differ between sexes, and (iii) identify risk-based, sex-specific thresholds for the quantitative parameters of regurgitation severity as well as RV and TA remodelling in patients with STR.

Methods

Study population

This retrospective analysis reviews echocardiographic studies collected from consecutive euvolemic outpatients with moderate and severe STR, acquired prospectively between October 2020 and March 2023 (FUTURE 3DECHO, ClinicalTrials.gov Identifier: NCT05747404). Exclusion criteria were primary TR, cardiac implantable electronic device-related TR, previous surgical/transcatheter tricuspid valve (TV) interventions, inadequate echocardiographic images, and follow-up length less than 6 months. This study was approved by the Ethics Committee of the Istituto Auxologico Italiano, IRCCS (record#2021_05_18_13, approved on 18 May 2021). The investigation conforms with the principles outlined in the Declaration of Helsinki.

Echocardiography

Patients underwent standard 2D and 3D echocardiography using Vivid E9/E95 (GE Healthcare, Horten, Norway) with 4V/4Vc probes. Images were analysed offline with EchoPAC-204 by two researchers (M.T. and D.N.R.) blinded to patients' medical history. Conventional echocardiographic parameters, including the pulmonary artery systolic pressure (PASP) and the size and function of the left atrium, right atrium (RA), RV, and left ventricle (LV), as well as the severity of aortic regurgitation or stenosis and mitral regurgitation (MR), were assessed in accordance with current recommendations.[5–7] The RV-focused apical view was used to assess RA volumes and longitudinal reservoir strain using the AFI LA software.[8,9] RV systolic function was assessed using (i) tricuspid annular plane systolic excursion (TAPSE), (ii) RV-free wall longitudinal strain obtained by applying the AFI RV software package, and (iii) RV ejection fraction (RVEF) calculated using the RV end-diastolic volume (RVEDV) and RV end-systolic volume (RVESV) measured with 4DAutoRVQ.[10] The TA diameter was measured in the standard apical four-chamber view at end-diastole.[11] In addition, the following parameters were also measured: the TA area, the major TA diameter, and the TA tenting volume (the volume enclosed by the TV leaflets and the TA surface in mid-systole) using dedicated 3D echocardiography datasets and software package (4DAutoTVQ).[12] Both STR effective regurgitant orifice area (EROA) and regurgitant volume (RegVol) were quantified by the corrected PISA method.[13,14] The regurgitant fraction (RegFr) was calculated by dividing the RegVol by the RV stroke volume, obtained as the difference between the RVEDV and RVESV.[13] The severity of STR was assessed by adopting the newly proposed five-grade severity scheme.[4]

Measurements were averaged from three consecutive cardiac cycles [five in patients with atrial fibrillation (AF)]. The differentiation between atrial and ventricular STR phenotypes was determined according to the recent recommendations.[4,15] Ventricular STR was further classified into left-sided cardiac disease, pulmonary hypertension (PH), and RV dysfunction.[16] We also estimated the risk of outcomes using the TRI-SCOREs.[17]

Follow-up and endpoint of the study

The primary endpoint was the occurrence of all-cause mortality or hospitalization for heart failure (HHF). Both all-cause mortality and HHF were also considered separately as secondary endpoints. Survival and hospitalization information was gathered through patient interviews and reviews of medical records every 6 months. Follow-up was censored at the time of the first event, defined as the occurrence of the composite outcome or the last follow-up for patients without clinical events. Assignment of clinical events was performed by physicians unaware of the patients' characteristics.

Statistical analysis

The distribution of continuous quantitative variables was assessed by the Shapiro–Wilk test. Continuous variables were presented as means with standard deviations or median with interquartile range as appropriate. Categorical variables were presented as numbers with percentages. Comparisons of continuous variables were done with either the Student's *t*-test or the Mann–Whitney *U* test as appropriate, whereas to compare binomial variables, we used the χ^2 test. Kaplan–Meier curves were used to estimate event-free survival rates, and differences between groups were analysed using the log-rank test. To adjust covariates between sexes, a propensity score inverse probability weighting (IPW) estimation was computed for each patient (see Supplementary data online, *Appendix*). To account for the competing risk of surgery, the Fine–Gray regression model was employed. This approach estimates the cumulative incidence function for the composite endpoint, providing subdistribution hazard ratio (sHR) with 95% confidence intervals (CIs). A univariate Cox regression model identified the factors associated with the composite endpoint, reporting HRs and CIs. Variables were entered into a multivariable analysis based on their clinical significance and/or significant association with outcomes in the univariable analysis. Sex-specific cut-offs for parameters assessing STR severity and RV and TA size and function were determined using Cox proportional hazards regression analyses with unadjusted restricted cubic splines for each echocardiographic variable. Splines were fitted with four knots placed at the 5th, 35th, 65th, and 95th percentiles, as determined by optimizing the Akaike information criterion. The sex-specific threshold for each variable was identified as the point where the HR deviated from the reference value (e.g. HR = 1). Statistical analyses were performed using R (version 4.3.2; R Foundation for Statistical Computing), with a two-sided significance level of $P < 0.05$ considered significant.

Results

After applying the exclusion criteria, a total of 554 patients (51% women) were included in the final cohort (see Supplementary data online, *Figure S1*). Women were older ($P < 0.001$), had higher systolic blood pressure ($P = 0.005$), and had a higher prevalence of AF ($P = 0.008$). In contrast, men were more likely to have coronary artery disease, Stages IV–V chronic kidney disease (CKD) ($P = 0.005$), and significant MR ($P < 0.001$). The aetiology of MR differed by sex ($P = 0.003$), with secondary MR more prevalent in men and primary MR more common in women. Loop diuretics were used in 25% of patients at baseline, with no sex-related differences in prescription rates ($P = 0.955$) or median furosemide-equivalent doses {women: 35 mg [interquartile range (IQR) 25–75] vs. men: 31 mg [IQR 25–50]; $P = 0.936$}. Furthermore, both LV and RVEF were higher in women ($P < 0.001$ for both). Women also exhibited smaller RV, RA, and TA than

Table 1 Demographics and baseline characteristics of the study population

	Total ($n = 554$)	Women ($n = 285$)	Men ($n = 269$)	*P*-value
Clinical characteristics				
Age, years	74 ± 13	78 ± 11	71 ± 14	**<0.001**
Body surface area, m^2	1.79 ± 0.22	1.67 ± 0.18	1.91 ± 0.18	**<0.001**
Systolic blood pressure, mmHg	127 ± 22	130 ± 22	124 ± 21	**0.005**
Diastolic blood pressure, mmHg	75 ± 13	76 ± 12	74 ± 13	0.190
Hypertension, *n* (%)	367 (66)	199 (70)	168 (62)	0.067
Chronic kidney disease (GFR < 30 mL/min), *n* (%)	147 (26)	61 (21)	86 (32)	**0.005**
Diabetes mellitus, *n* (%)	118 (21)	55 (19)	63 (23)	0.236
Chronic obstructive pulmonary disease, *n* (%)	248 (45)	124 (43)	124 (46)	0.540
Coronary artery disease, *n* (%)	93 (18)	57 (20)	36 (15)	**<0.001**
AF, *n* (%)	320 (58)	180 (63)	140 (52)	**0.008**
Type of AF				0.227
Paroxysmal AF, *n* (%)	75 (13)	42 (15)	33 (12)	
Persistent AF, *n* (%)	59 (11)	26 (8)	33 (12)	
Permanent AF, *n* (%)	191 (34)	103 (35)	88 (33)	
Left heart surgery, *n* (%)	73 (13)	42 (15)	31 (11)	0.264
Tricuspid valve interventions, *n* (%)	26 (5)	14 (5)	12 (4)	0.802
NYHA, *n* (%)				0.077
I–II	379 (67)	202 (71)	177 (66)	
III–IV	175 (33)	83 (29)	92 (34)	
Loop diuretics, *n* (%)	170 (31%)	87 (30%)	83 (30%)	0.954
TRI-SCORE	4.9 ± 2.3	4.0 ± 2.1	5.2 ± 2.2	**0.004**
Echocardiographic parameters				
Left ventricular ejection fraction, %	50 ± 15	56 ± 11	43 ± 15	**<0.001**
Left atrial volume indexed, mL/m^2	59 ± 26	59 ± 27	58 ± 26	0.850
E/e′	12.5 ± 5.4	12.3 ± 5.2	12.6 ± 5.5	0.543
TAPSE, mm	17 ± 4	17 ± 4	17 ± 4	0.256
RV-free wall longitudinal strain, %	19.2 ± 6.8	20.9 ± 6.3	17.4 ± 6.8	**<0.001**
RV end-diastolic volume indexed, mL/m^2	87 ± 31	81 ± 29	93 ± 32	**<0.001**
RV end-systolic volume indexed, mL/m^2	44 ± 23	38 ± 21	50 ± 23	**<0.001**
RV ejection fraction, %	51 ± 11	55 ± 10	47 ± 11	**<0.001**
PASP, mmHg	43 ± 16	44 ± 16	42 ± 15	0.378
Right atrial volume indexed, mL/m^2	55 ± 31	53 ± 29	58 ± 32	**0.039**
Right atrial reservoir strain, %	13 (8–22)	13 (9–24)	12 (7–19)	**0.004**
Tricuspid annulus four-chamber, mm	38.5 ± 6.0	36.7 ± 4.9	40.4 ± 6.4	**<0.001**
Tricuspid annulus four-chamber indexed, mm/m^2	21.7 ± 3.8	22.2 ± 3.7	21.3 ± 3.8	**0.006**
Tricuspid annulus 3D (major axis), mm	47.7 ± 7.7	45.7 ± 6.8	49.8 ± 8.1	**<0.001**
Tricuspid annulus area 3D, mm^2	14.9 ± 4.7	13.6 ± 4.3	16.3 ± 4.8	**<0.001**
Tricuspid valve tenting volume 3D, mL	2.9 (1.8–4.6)	2.3 (1.4–3.7)	3.6 (2.4–5.3)	**<0.001**
TR effective regurgitant orifice area, cm^2	0.34 (0.22–0.48)	0.34 (0.23–0.44)	0.33 (0.22–0.53)	0.522
TR regurgitant volume, mL	32 ± 17	31 ± 14	34 ± 20	0.098
TR regurgitant fraction, %	42 ± 16	43 ± 15	41 ± 17	0.078
Secondary TR phenotypes				**<0.001**
Ventricular, *n* (%)	341 (61)	134 (47)	207 (77)	
Left-sided cardiac disease, *n* (%)	280 (50)	95 (34)	185 (69)	
Pulmonary hypertension, *n* (%)	41 (7)	27 (9)	14 (5)	
RV dysfunction, *n* (%)	20 (4)	12 (4)	8 (3)	
Atrial, *n* (%)	213 (39)	151 (53)	62 (23)	

Continued

Table 1 Continued

	Total ($n = 554$)	Women ($n = 285$)	Men ($n = 269$)	*P*-value
TR grade, *n* (%)				0.241
2	326 (59)	171 (60)	155 (58)	
3	140 (25)	77 (27)	63 (23)	
4	52 (9)	23 (8)	29 (11)	
5	36 (7)	14 (5)	22 (8)	
Mitral regurgitation grade, *n* (%)				**<0.001**
0–1	310 (56)	176 (62)	134 (50)	
2–3	244 (44)	109 (38)	135 (50)	
Mitral regurgitation phenotypes				**0.003**
Primary, *n* (%)	139 (25)	87 (31)	52 (19)	
Secondary, *n* (%)	415 (75)	198 (69)	217 (81)	
Aortic regurgitation grade, *n* (%)				0.453
0–1	508 (91)	263 (92)	245 (91)	
2–3	46 (9)	22 (8)	22 (9)	
Aortic stenosis grade, *n* (%)				0.652
0–1	516 (93)	262 (92)	254 (94)	
2–3	38 (7)	23 (8)	15 (6)	

Bold values represent $P < 0.05$. AF, atrial fibrillation; GFR, glomerular filtration rate; NYHA, New York Heart Association; RV, right ventricular; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

men. Atrial STR was more prevalent in women than in men ($P < 0.001$) Finally, women showed lower TRI-SCOREs than men (4.1 ± 2.1 vs. 5.2 ± 2.2, respectively; $P = 0.004$) (*Table 1*).

Survival analysis stratified by sex

After a median follow-up of 19 (8–27) months, 230 patients met the combined endpoint (153 HHF and 119 deaths). Within the first year of follow-up, 45 of 269 men (16.7%) and 30 of 285 women (10.5%) died, while HHF occurred in 55 men (20.4%) and 55 women (19.3%). Notably, 50% of the events occurred within a median time of 9 months in men and 8 months in women (see Supplementary data online, *Figure S2*). At the 2-year follow-up, women and men exhibited similar risk of experiencing the composite endpoint (HR, 1.25; 95% CI, 0.96–1.62; $P = 0.097$), even after IPW (IPW-HR, 1.06; 95% CI, 0.69–1.63; $P = 0.789$) (*Graphical Abstract, Panels A* and *B*). Similar results were also obtained when accounting for the competing risk of TV surgical/transcatheter interventions (sHR, 1.22; 95% CI, 0.94–1.58; $P = 0.13$). Supplementary data online, *Figures S3* and *S4* show the Kaplan–Meier curves for individual endpoints. Although men exhibited higher unadjusted mortality at 2 years, no significant sex differences were observed for all-cause death or HHF after IPW. After adjustment for sex, age was not significantly associated with mortality (aHR, 1.001; 95% CI, 0.991–1.011; $P = 0.864$), and no significant interaction was observed between age and sex in the Cox model ($P = 0.21$). Finally, when stratified according to STR phenotypes, the PH phenotype experienced the lowest survival rate in both sexes (*Figure 1*).

During the follow-up, 14 women and 12 men underwent TV surgical/percutaneous treatments ($P = 0.802$).

Supplementary data online, *Table S1* presents the univariate Cox regression analysis. After considering the correlations among the variables (see Supplementary data online, *Figure S5*), multivariate Cox regression analysis revealed that, besides EROA that was associated with the composite endpoint in both sexes, the other variables independently associated with the composite endpoint at the 2-year follow-up were sex specific, including New York Heart Association (NYHA) Classes III–IV($P < 0.001$), CKD Stages IV–V($P = 0.019$), RVEDV($P = 0.012$), and TV tenting volume ($P = 0.011$) for women and RA volume ($P < 0.001$) and RVEF ($P = 0.002$) for men (*Table 2*). Multivariable Cox regression analyses for individual endpoints are presented in Supplementary data online, *Table S2*. Finally, the PH phenotype was not associated with the composite endpoint in both sexes (see Supplementary data online, *Table S3*).

Identifying outcome-based, sex-specific thresholds for STR severity and RV and TA remodelling

The spline-derived cut-offs for an increased risk of adverse events were lower in women compared with men for both EROA (0.36 cm^2 vs. 0.43 cm^2) (*Figure 2*) and RegVol (31 mL vs. 35 mL) (see Supplementary data online, *Figure S6*). In contrast, women had a higher cut-off for RegFr (46% vs. 39%) (*Figure 2*). When assessing non-sex-specific cut-offs for STR severity, women demonstrated higher risk than men for EROA > 0.4 cm^2, RegVol > 45 mL, and RegFr > 50% (*Figure 3*).

Both men and women demonstrated a non-linear relationship between increasing RVEDVi and RVESVi and the composite endpoint (*Figure 2*). However, the inflection point for increased HRs occurred at lower thresholds in women compared with men: 81 mL/m^2 vs. 96 mL/m^2 for RVEDVi and 37 mL/m^2 vs. 49 mL/m^2 for RVESVi (*Figure 2*). At a larger extent of RV remodelling, women exhibited a steeper increase in HR compared with men. Lower RVEF was associated with higher risk in both sexes, with similar slopes of the spline curves. However, the inflection point with HR = 1 occurred at a higher RVEF in women compared with men (49% vs. 41%) (*Figure 2*). The spline-derived cut-offs for TAPSE (18.5 mm for both sexes) and

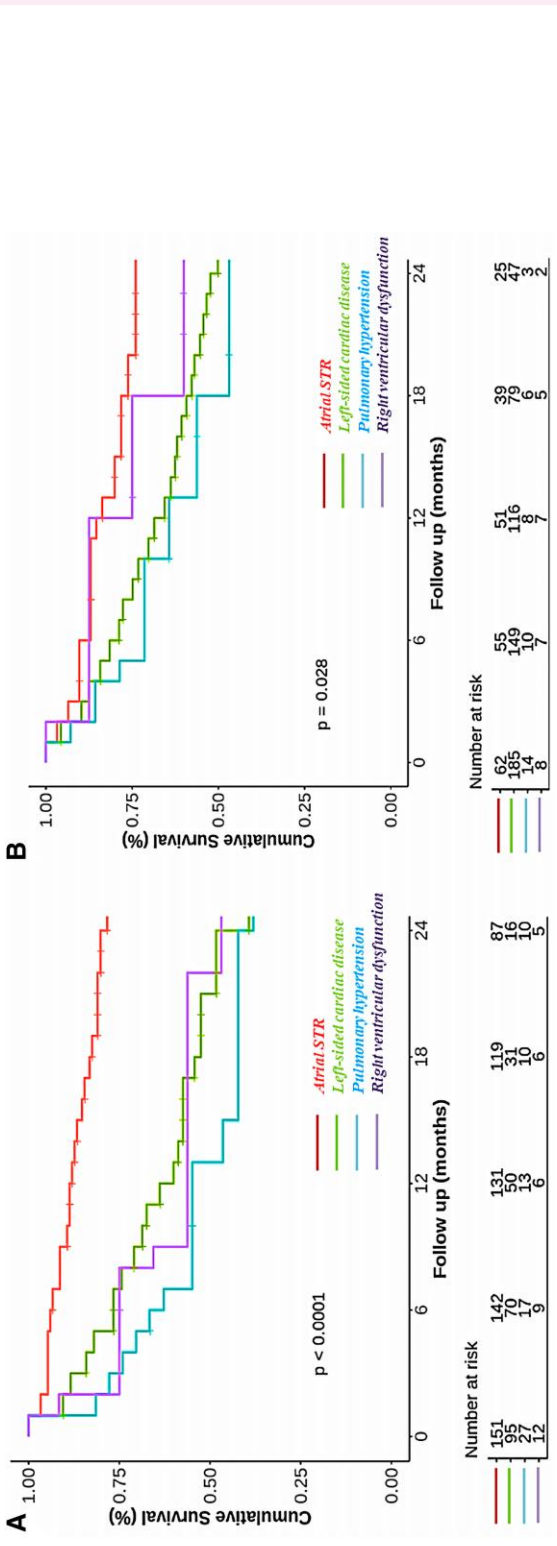


Figure 1 Kaplan–Meier curves illustrating event-free survival in men (*A*) and women (*B*), stratified by STR phenotypes. STR, secondary tricuspid regurgitation.

RV-free wall longitudinal strain (19% for men and 20% for women) were similar between sexes (see Supplementary data online, *Figure S6*). When assessing non-sex-specific cut-offs for RV remodelling based on TVARC,[4] women demonstrated higher HRs than men for RVEDVi ≥ 95 mL/m^2, RVESVi ≥ 37 mL/m^2, and RVEF < 45% (*Figure 3*).

Patients with larger RVEDVi and RVESVi and lower RVEF had a lower survival probability at 2 years, regardless of sex, with a more pronounced decline in those with severe STR. Notably, women exhibited worse outcomes than men at comparable RV function and volumes, especially in patients with moderate STR (*Figure 4*).

The thresholds values of TA geometry associated with increased HR defined for men and women were 40 mm (22 mm/m^2) vs. 37 mm (19 mm/m^2) for the four-chamber TA diameter, 51 mm vs. 46 mm for the 3D-TA major axis, 17 cm^2 vs. 14 cm^2 for the 3D-TA area, and 3.3 mL vs. 2.1 mL for the 3D-TV tenting volume (*Figure 2*; Supplementary data online, *Figure S6*). When using the cut-offs of TA dilation recommended by guidelines,[4–6] we observed higher HRs for men with a four-chamber indexed TA diameter > 21 mm/m^2. However, this trend was not observed for a four-chamber TA diameter ≥ 40 mm (*Figure 3*).

Discussion

This is the first study to identify the sex-specific echocardiographic thresholds for regurgitation severity and RV and TA remodelling that are associated with outcomes in patients with STR. The main findings of our study are as follows: (i) men and women with STR under medical treatment have the same incidence of all-cause mortality and HHF; (ii) with the exception of the EROA, the clinical and echocardiographic parameters associated with outcomes differed between sexes; and (iii) in women, the risk of experiencing the composite endpoint is comparable to that of men at lower EROAs, smaller RegVol, smaller RVs and TA, and higher RegFr and RVEF.

Sex differences in clinical presentation, aetiology, and right heart remodelling in STR

In our study, event rates were comparable between men and women after adjustment for covariates, both for the composite endpoint of death and HHF, as well as for each individual endpoint. Our data align with Dietz *et al.*[3] who found similar death rates between sexes after applying propensity score matching.

In our cohort, women were older, had a greater prevalence of AF, and exhibited a trend towards higher prevalence of arterial hypertension. These factors, along with obesity, are commonly associated with an increased risk of HF with preserved EF (HFpEF).[18] Recent evidence highlights a strong association between the risk of HFpEF and significant STR,[19] explaining the higher prevalence of atrial STR observed in women compared with men.[2,3,20] In contrast, men were more likely to present LV dysfunction associated with coronary artery disease or significant left-side valvular heart diseases, and moderate-to-severe CKD.[2,3,20] Consequently, ventricular STR was more prevalent in men.

However, age did not influence the mortality risk in our cohort. Moreover, although the PH phenotype was characterized by the lowest survival rates in both sexes,[16] neither PH nor the echocardiographic estimation of PASP was independently associated with outcomes. This finding underscores the limited accuracy of echocardiography compared with right heart catheterization for identifying PH in patients with significant STR.[21]

Regarding the echocardiographic parameters, our findings revealed that women, in the presence of similar RegVol, exhibited smaller RV and RA volumes, as well as reduced TA dimensions and TV tethering.[2] Notably, women had higher RA strain values and showed less

Table 2 Cox regression hazard models comparing the associations between clinical and echocardiographic parameters and outcomes, stratified by sex

	Men		Women	
	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
NYHA Classes III–IV	1.43 (0.92–2.20)	0.108	2.21 (1.41–3.47)	**<0.001**
Chronic kidney disease (GFR < 30 mL/min)	1.50 (0.98–2.32)	0.063	1.70 (1.09–2.66)	**0.019**
Right atrial volume, 1 mL/m^2 increment	1.01 (1.01–1.02)	**<0.001**	1.00 (0.99–1.01)	0.798
Right atrial reservoir strain, 1% decrement	1.00 (0.98–1.03)	0.846	1.01 (0.99–1.04)	0.205
RV end-diastolic volume, 1 mL/m^2 increment	0.99 (0.98–1.00)	0.057	1.01 (1.00–1.02)	**0.012**
RV ejection fraction, 1% decrement	1.05 (1.02–1.08)	**0.002**	1.01 (0.98–1.04)	0.588
Left ventricular ejection fraction, 1% decrement	0.99 (0.97–1.01)	0.215	1.00 (0.98–1.02)	0.776
Tricuspid annulus 3D (major axis), 1 mm increment	1.00 (0.98–1.02)	0.972	1.00 (0.96–1.04)	0.964
Tricuspid valve tenting volume 3D, 1 mL increment	1.05 (0.99–1.11)	0.116	0.87 (0.78–0.97)	**0.011**
TR effective regurgitant orifice area, 0.1 cm^2 increment	1.08 (1.02–1.16)	**0.013**	1.13 (1.01–1.25)	**0.028**
PASP, 1 mmHg increment	1.01 (1.00–1.03)	0.068	1.01 (1.00–1.02)	0.162

Bold values represent $P < 0.05$. Abbreviations as in *Table 1*.

impairment in both RV longitudinal and global pump functions. In the multivariate Cox regression analysis, NYHA Classes III–IV, moderate-to-severe CKD, RVEDV, and 3D-TV tenting volume were significantly associated with outcomes in women. In contrast, in men, the covariates significantly associated with outcomes were RA volume and RVEF. Notably, STR severity, assessed by EROA, was associated with outcomes in both sexes, underscoring its independent prognostic value regardless of age, sex, and other variables.[22] Our results aligns with Fortmeier *et al.*[20] who identified NYHA class, CKD, and RV dysfunction as predictors in women. In contrast, NYHA class and pulmonary vascular resistance emerged as predictors of 2-year mortality following transcatheter TV interventions. Notably, in that study preprocedural TR severity was associated with mortality only in men.

In our cohort, we found no differences in the quantitative parameters used to assess STR severity. Similarly, previous studies[3,20] reported no sex-based differences in the EROA. However, Dietz *et al.*[3] observed that women had a significantly lower RegVol. This finding is likely explained by the higher prevalence of atrial STR in women, which is associated with smaller ventricles and lower RegVols.[15]

Should sex-specific cut-offs be used to improve risk stratification in STR?

So far, no studies have yet emphasized the need for sex-specific, risk-based thresholds for STR severity. We demonstrated that women had lower cut-offs for the EROA (0.36 cm^2 vs. 0.43 cm^2) and RegVol (31 mL vs. 35 mL) but a higher RegFr (46% vs. 39%). Our findings that align with a previous study[23] on primary MR found that women had lower EROAs, smaller RegVols, and smaller ventricular volumes than men. The thresholds for RegVol and EROA associated with adverse LV remodelling were consistently lower in women. Additionally, for the same RegFr, women had significantly lower RegVols than men.

In the past, RV size and function were predominantly evaluated through visual inspection or using simple echocardiographic parameters.[2] However, the recent adoption of transcatheter TV repair techniques has necessitated the standardization of RV assessment in patients with TR.[24] In this regard, the TVARC[4] established normative values for RV size and function.[25] The upper limits of normal for RVEDV and RVESV were defined as 95 mL/m^2 and 43 mL/m^2, respectively, while the lower limit of normal for RVEF was set at 45%, as measured by 3D echocardiography. Notably, these reference values were based on men and were significantly higher than those for women, whose upper limits for RVEDV and RVESV were 81 mL/m^2 and 36 mL/m^2, respectively.

However, the TVARC thresholds were derived from healthy subjects[25] and were not based on the specific risk of adverse events in patients with STR. Recently, in our cohort of 513 patients with moderate-to-severe STR, we identified the following thresholds as being significantly associated with outcomes: RVEDV > 90 mL/m^2, RVESV > 46 mL/m^2, and RVEF < 45%.[26] Our data demonstrate that, while both men and women showed a significant relationship between increasing RV volumes, decreasing RVEF, and mortality or HHF, the thresholds for excessive risk differed between sexes. Specifically, women had lower thresholds for RVEDV (81 mL/m^2 vs. 96 mL/m^2) and RVESV (37 mL/m^2 vs. 49 mL/m^2), but higher thresholds for RVEF (49% vs. 41%). Moreover, when using the TVARC criteria,[4] women have a higher likelihood of experiencing adverse events for the same degree of RV dilation or dysfunction.

Clinical application

Our findings indicate that, although the overall rate of adverse events did not differ significantly between sexes, women experienced a comparable risk despite exhibiting less advanced TR-induced right heart remodelling. This suggests that waiting for women to meet current TV intervention criteria, such as EROA > 0.4 cm^2, RegVol > 45 mL, RVEDV > 95 mL/m^2, RVESV > 43 mL/m^2, or RVEF < 45%, may result in more pronounced structural and functional deterioration compared with men. Therefore, our analysis supports a personalized, sex-specific approach to STR severity assessment, emphasizing the need for tailored threshold values.

Limitations

This retrospective analysis included only patients with high-quality imaging, allowing for precise assessment of RV volumes and systolic function using 3D echocardiography, which may introduce selection bias. The lack of systematic adjudication of cause-specific mortality

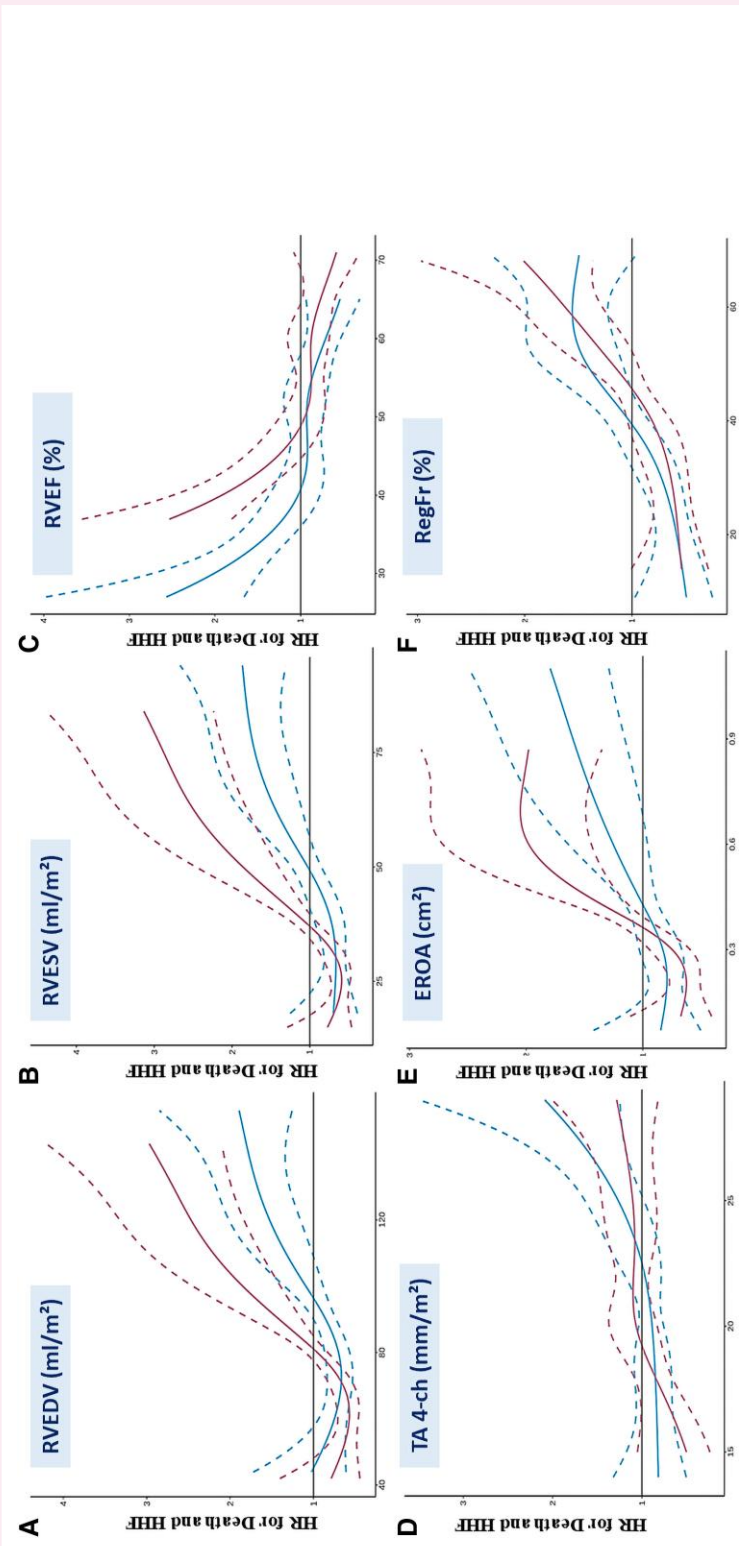


Figure 2 Sex-specific cut-offs for STR severity and RV and TA parameters associated with death and HHF. (*A–F*) Spline curves illustrating the risk of death and HHF based on STR severity and RV/TA parameters, stratified by sex. Abbreviations as in Graphical Abstract.

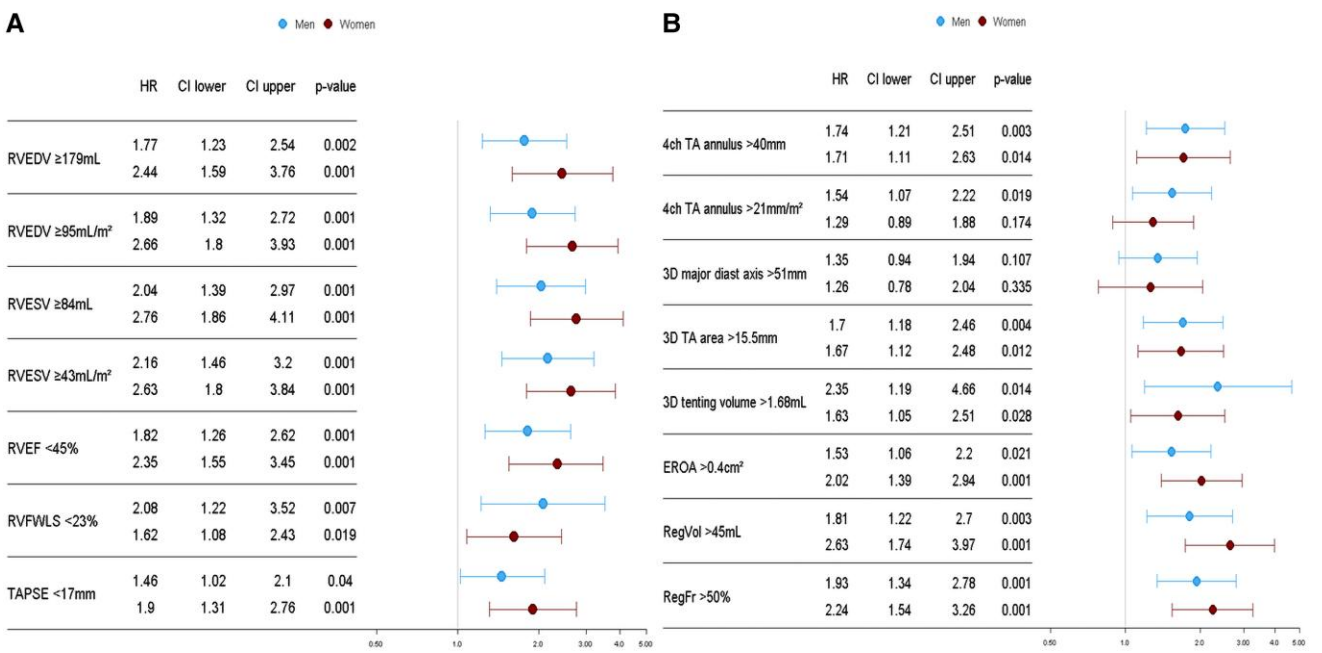


Figure 3 Sex-specific HRs for RV and TA parameters associated with the composite endpoint using TVARC[4] and guidelines[5,6] criteria. Forest plots illustrating the excess risk of the composite endpoint linked to RV (*A*) as well as STR severity and TA (*B*) parameters stratified by sex. EDV, end-diastolic volume; ESV, end-systolic volume; RVFWLS, right ventricular free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; the other abbreviations as in Graphical Abstract.

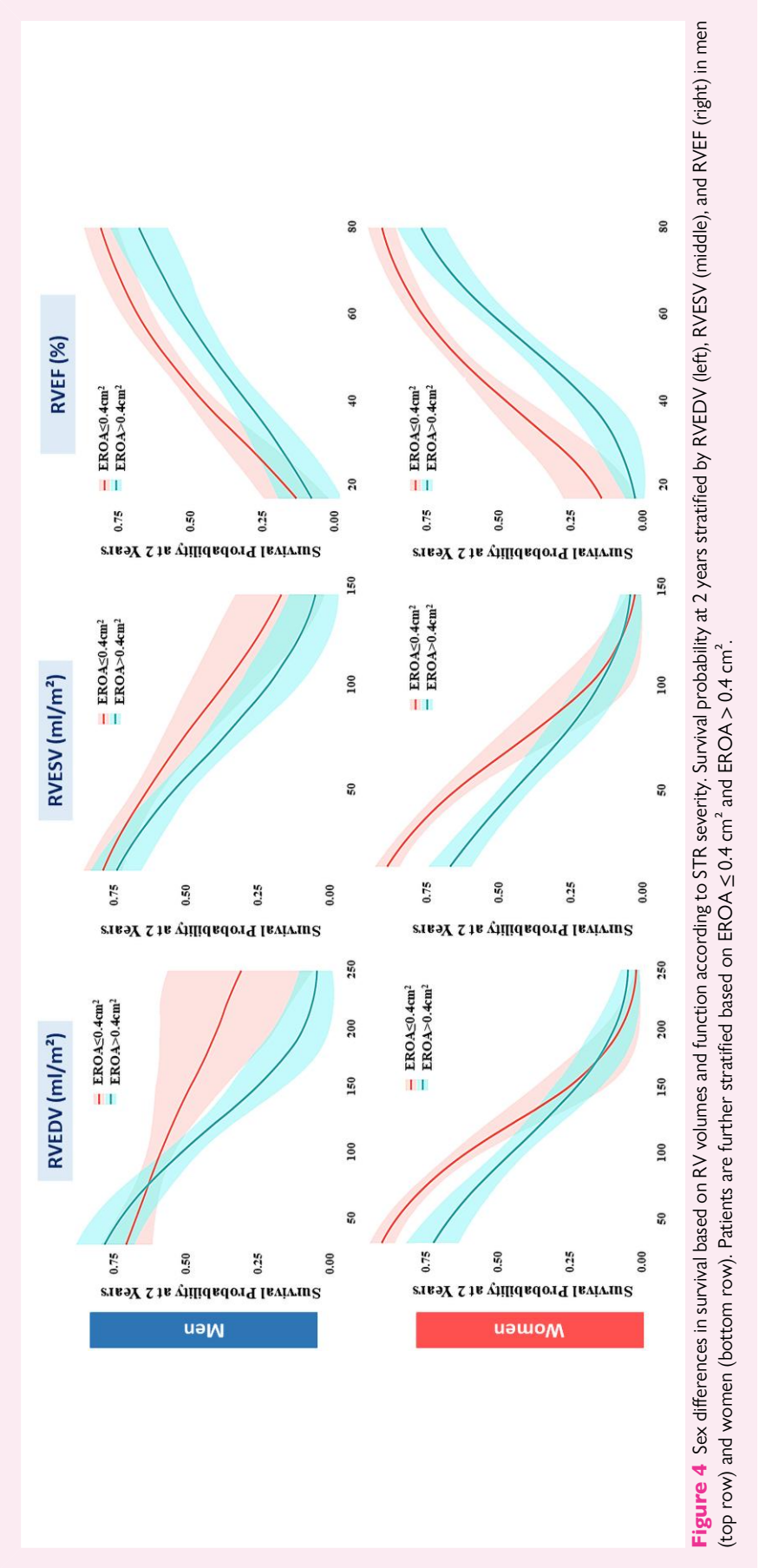


Figure 4 Sex differences in survival based on RV volumes and function according to STR severity. Survival probability at 2 years stratified by RVEDV (left), RVESV (middle), and RVEF (right) in men (top row) and women (bottom row). Patients are further stratified based on EROA ≤ 0.4 cm^2 and EROA > 0.4 cm^2.

precluded reliable differentiation between cardiovascular and non-cardiovascular deaths; however, the use of all-cause mortality as an endpoint is aligned with TVARC recommendations.[4] The low rate of TV intervention in our cohort reflects current guideline recommendations, which often delay intervention until advanced disease, the high surgical risk associated with isolated TR, and the limited availability of transcatheter therapies during the study period.[4–6] The incomplete availability of B-type natriuretic peptide data in our cohort precluded a comprehensive evaluation of the biomarker's impact stratified by sex. Given the limited feasibility of RV outflow tract Doppler measurements in our cohort and the high prevalence of multiple valvular regurgitations, we selected a validated combination of corrected PISA and 3D volumetric methods to ensure consistent and reliable quantification of RegFr across all patients.[13] Future multicentre prospective studies and trials are needed to better understand sex differences and improve outcomes in women.

Conclusion

Despite a similar survival rate between sexes in patients with significant STR, women showed differences in underlying aetiology, the extent of right heart remodelling, and the variables associated with adverse outcomes, as well as the thresholds for increasing risk. Our study suggests that women may benefit from different STR severity parameters cut-offs, as well as absolute and indexed cut-offs for RV and TA dimensions. Furthermore, our results indicate that waiting for a similar drop in RVEF may cause more excessive long-term harm in women compared with men.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: L.P.B. and D.M. are members of the speaker bureaus of GE Healthcare and Philips Medical Systems and received research grants from GE Healthcare, Philips Medical Systems, TomTec Imaging Systems, and Esaote SpA. M.T. and A.C. received research grants from Philips. D.M. and M.-A.C. serve as associate editors for the *European Heart Journal—Cardiovascular Imaging*. The remaining authors have nothing to disclose.

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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