Characterization of tricuspid regurgitation and its prognostic implications

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Part I

The right ventricle in secondary tricuspid regurgitation

Chapter 2

Prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation

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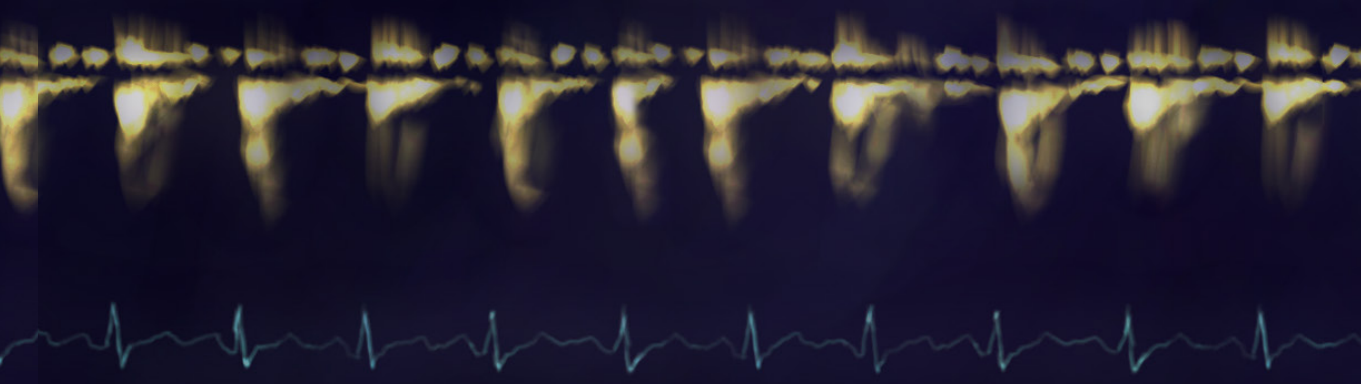


ABSTRACT

Background: In patients with significant (moderate and severe) tricuspid regurgitation (TR), the decision to intervene is influenced by right ventricular (RV) size and function. RV remodeling in significant secondary TR has been underexplored. The aim of this study was to characterize RV remodeling in patients with significant secondary TR and to investigate its prognostic implications.

Methods: RV remodeling was characterized by transthoracic echocardiography in 1292 patients with significant secondary TR (median age 71 (62-78), 50% male). Four patterns of RV remodeling were defined according to the presence of RV dilation (tricuspid annulus≥40mm) and RV systolic dysfunction (<17 mm): pattern 1) normal RV size and systolic function; pattern 2) dilated RV with preserved systolic function; pattern 3) normal RV size with systolic dysfunction; pattern 4) dilated RV systolic dysfunction. The primary endpoint was all-cause mortality and the event rates were compared across the 4 patterns of RV remodeling.

Results: A total of 183 (14%) patients showed pattern 1 RV remodeling, 256 (20%) showed pattern 2, 304 (24%) presented with pattern 3 and 549 (43%) had pattern 4 RV remodeling. Patients with pattern 4 RV remodeling were more frequently male, more often had coronary artery disease, worse renal function, impaired left ventricular ejection fraction and were more often symptomatic. Only 98 (8%) patients underwent tricuspid valve annuloplasty during follow-up. During a median follow-up of 34 (IQR 0-60) months, 510 (40%) patients died. The 5-year survival rate was significantly worse in patients presenting with patterns 3 and 4 RV remodeling compared with pattern 1 (52% and 49% vs. 70%; p=0.002 and p<0.001, respectively), and were independently associated with poor outcome on multivariable analysis.

Conclusion: In patients with significant secondary TR, patients with RV systolic dysfunction have worse clinical outcome regardless of the presence of RV dilation.

INTRODUCTION

The prognosis of patients with significant tricuspid regurgitation (TR) is strongly influenced by right ventricular (RV) dilation and dysfunction. The volume overload caused by significant TR leads to further dilation and dysfunction of the right ventricle (1-3). However, this RV remodeling process has not been fully evaluated and whether RV dilation and dysfunction may or may not coexist remains unknown. The two components of RV remodeling (dilation and dysfunction) may also have different impact on prognosis.

Based on current guidelines, tricuspid valve surgery is indicated in patients with severe TR undergoing left-sided valve surgery (class IC) and in patients with previous left-sided valve operation who have developed symptomatic severe secondary TR with progressive RV dilation in the absence of RV or left ventricular (LV) systolic dysfunction (class IIaC) (4, 5). Therefore, assessment of RV dimensions and function is crucial to select patients who may benefit from surgical tricuspid valve intervention. Current recommendations on chamber quantification with echocardiography provide cut-off values to define RV dilation and dysfunction (2, 4-9). However, these values are based on normal individuals without any history of heart disease. The values of RV dimensions and function in patients with significant secondary TR remain largely unexplored and the frequency of RV dilation with and without RV dysfunction has not been reported. Accordingly, the present study (including a large group of patients with significant secondary TR) aimed at characterizing RV remodeling and evaluating the prognostic impact of RV dilation and RV dysfunction on long-term survival.

METHODS

Patient population

The data that support the findings of this study are available upon reasonable request to the corresponding author. Patients with significant (moderate and severe) secondary TR were selected from the departmental echocardiographic database at the Leiden University Medical Center (Leiden, the Netherlands) between June 1995 and September 2016 by performing a query. TR severity was classified according to current guidelines by an integrative approach based on qualitative, semiquantitative and quantitative color Doppler flow data, continuous wave Doppler data of the regurgitant jet and assessment of right ventricular and atrial dimensions (8). Patients with primary TR (valve prolapse, active endocarditis, acute rheumatic disease or tumor) and congenital heart disease were excluded. In addition, patients with incomplete echocardiographic data to assess RV remodeling were excluded. Patients were evaluated with transthoracic echocardiography

in order to assess RV size (measured by tricuspid annular [TA] diameter) and RV systolic function (measured by tricuspid annular plane systolic excursion [TAPSE]) (2, 3).

Demographics and clinical data were collected in the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center, Leiden, the Netherlands) and analyzed retrospectively. This retrospective analysis of clinically acquired data was approved by the institutional review board of the Leiden University Medical Center and the need for patient written informed consent was waived.

Clinical and echocardiographic variables

Baseline demographic, clinical and laboratory variables were evaluated at the time of first diagnosis of moderate or severe TR by transthoracic echocardiography. Clinical characteristics included symptoms of heart failure (dyspnea and peripheral edema), cardiovascular risk factors, hemoglobin level, creatinine level and medication. Body surface area (BSA) was calculated using the Mosteller method (10). Coronary artery disease was defined as previous myocardial infarction or significant stenosis of an epicardial coronary artery (>70%) diagnosed by invasive coronary angiogram.

Transthoracic echocardiographic data were obtained with patients at rest using available ultrasound systems (Vivid 7 and E9 systems; GE-Vingmed, Horton, Norway) equipped with 3.5Mhz or M5S transducers, adjusting gain and depth settings. All images were digitally stored for offline analysis with commercially available software (EchoPAC version 113.0.3 and 202; GE-Vingmed, Horten, Norway). M-mode, bidimensional and color, continuous and pulsed wave Doppler data were acquired on the parasternal, apical and subcostal views according to current guidelines (7-9, 11). LV volumes were measured on the apical 2- and 4-chamber views according to the Simpson's method and LV ejection fraction (LVEF) was derived (6). LVEF was categorized into preserved (≥50%), mid-range (40-49%) and reduced (<40%) according to the current guidelines (12). The TA diameter acquired on a focused RV apical view was evaluated to reflect RV remodeling. Furthermore, RV dimensions, RV end-systolic and end-diastolic areas were acquired on an RV focused apical view. All ventricular and atrial size measurements were indexed for BSA. RV systolic function was quantified based on TAPSE measured on M-mode recordings of the lateral tricuspid annulus in a focused RV apical view. TR grade was assessed by a multi-parametric approach including qualitative, semiquantitative and quantitative parameters measured on bidimensional, color, continuous and pulsed wave Doppler data as recommended by recent guidelines (8). Systolic pulmonary artery pressures were estimated from the

tricuspid regurgitant jet peak velocity applying the Bernoulli equation and adding 3, 8 or 15 mmHg based on inferior vena cava collapsibility (7).

Follow-up and outcome definition

All patients were followed-up for the occurrence of all-cause mortality (primary endpoint). Survival data were ascertained from the departmental Cardiology Information System and the Social Security Death Index and were complete for all patients. In addition, the occurrence of tricuspid valve surgery (repair or replacement) was recorded (secondary endpoint).

Statistical analysis

Continuous variables are presented as mean ± standard deviation in case of Gaussian distribution and as median (interquartile range) if not normally distributed. Categorical variables are presented as frequencies and percentages.

To assess the hazard ratio (HR) change for all-cause mortality across a range of TA diameters and TAPSE, spline curves analysis was performed. The cut-off values of TA diameter and TAPSE associated with excess of mortality were used to define 4 groups of RV remodeling patterns based on dilation of the RV and RV systolic dysfunction:

- Pattern 1 comprised of all patients with a normal RV size and normal systolic function.
- Pattern 2 consisted of patients with a dilated RV with preserved systolic function.
- Pattern 3 included all patients with a non-dilated RV with systolic dysfunction.
- Pattern 4 comprised of patients with a dilated RV with systolic dysfunction.

Differences among the 4 patterns of RV remodeling were analyzed using the one-way analysis of variance (ANOVA) for continuous variables with Gaussian distribution, the Kruskal-Wallis test for non-normally distributed continuous variables and the Pearson's chi-square test for categorical variables. Multiple comparisons for continuous variables were tested with the Bonferroni correction.

The Kaplan-Meier curves were used to estimate the 1- and 5-year survival rates and differences between groups were analyzed using the log-rank test. A multivariable Cox proportional hazards regression analysis was performed to assess the clinical and echocardiographic factors that were independently associated with all-cause mortality. Possible confounders with a significant p-value ($p<0.05$) in the univariable analysis were included in the multivariable regression analysis. HR and 95% confidence intervals (CI)

were calculated. P-values <0.05 were considered significant. All data were analyzed with SPSS for Windows, version 23 (SPSS Inc, Armonk, NY:IBM Corp).

RESULTS

Patient population and definition of patterns of RV remodeling

Of the 1,292 patients with significant secondary TR included in the analysis (median age 71 years, IQR 62-78 years, 50% male), 1,020 (79%) had moderate TR and 272 (21%) had severe TR (Figure 1). Based on spline curve analysis, the assumption of linearity for all-cause mortality, predicted from the baseline TA diameter and TAPSE, was not violated ($\chi 2$: 5.75, p= 0.131 and $\chi 2$: 3.25, p= 0.360, respectively) i.e. demonstrating a non-linear relation of these variables with all-cause mortality. For TA diameter, an increase of HR

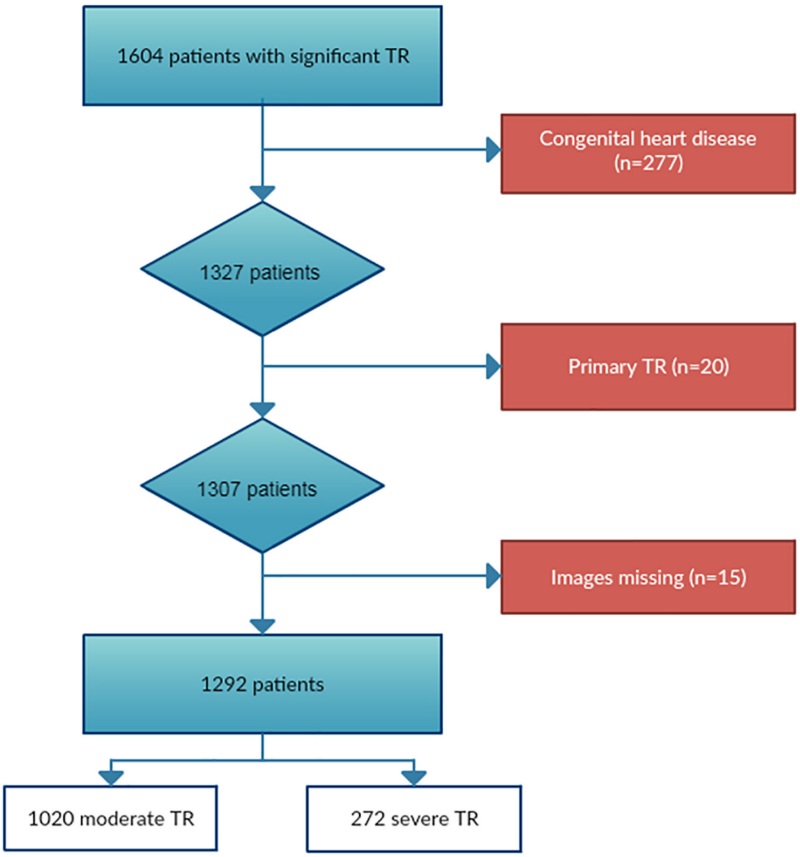


Figure 1. Flowchart of inclusion of patients with significant secondary tricuspid regurgitation
TR = tricuspid regurgitation

can be observed at 40 mm after an initial plateau phase (Figure 2). An inverted trend can be observed for TAPSE, where after a slow rise of HR, there is an increase in relative risk for values of 17 mm and lower (Figure 2). These spline curves suggest that the values of 40 mm for TA diameter and 17 mm for TAPSE are appropriate thresholds for dichotomizing the study population. Therefore, based on these cut-off values, 4 patterns of RV remodeling were defined as shown in Figure 3. The distribution of RV remodeling patterns in the population is shown in Figure 4: 183 (14%) patients showed pattern 1 (no RV dilation, no RV dysfunction), 256 (20%) patients showed pattern 2 (RV dilation but no RV dysfunction), 304 (24%) presented with pattern 3 (no RV dilation but RV dysfunction) and 549 (43%) had pattern 4 (RV dilation and dysfunction). No significant differences were observed in the distribution of RV remodeling patterns between moderate and severe TR (p=0.183).

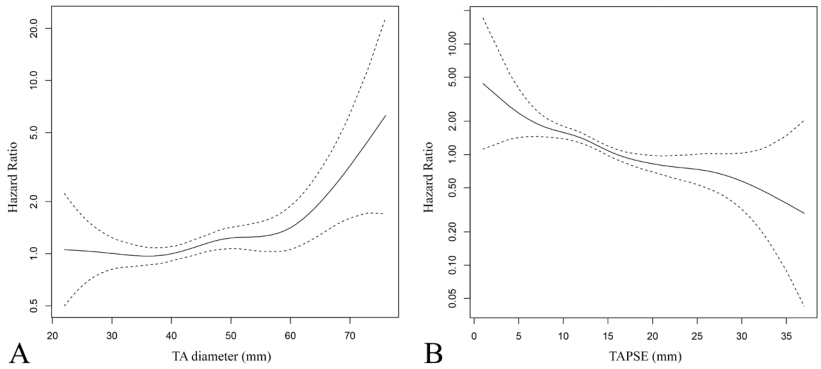


Figure 2. Spline curves for TA diameter and TAPSE vs. all-cause mortality

Changes in hazard ratio (HR) across the baseline tricuspid annulus diameter (2a) and TAPSE (2b) were demonstrated in spline curves on a hazards scale with overlaid 95% confidence intervals (dotted line) and shows the relationship of tricuspid annulus diameter and TAPSE and all-cause mortality.

TA = tricuspid annulus, TAPSE = tricuspid annular plane systolic excursion

Clinical characteristics

The clinical characteristics of the overall population and according to the different patterns of RV remodeling are shown in Table 1. Approximately half of the patients presented with dyspnea (52%) and peripheral edema was observed in 240 patients (21%). The use of diuretics was high (62%). Pacemaker leads were present in 464 patients (36%) and 590

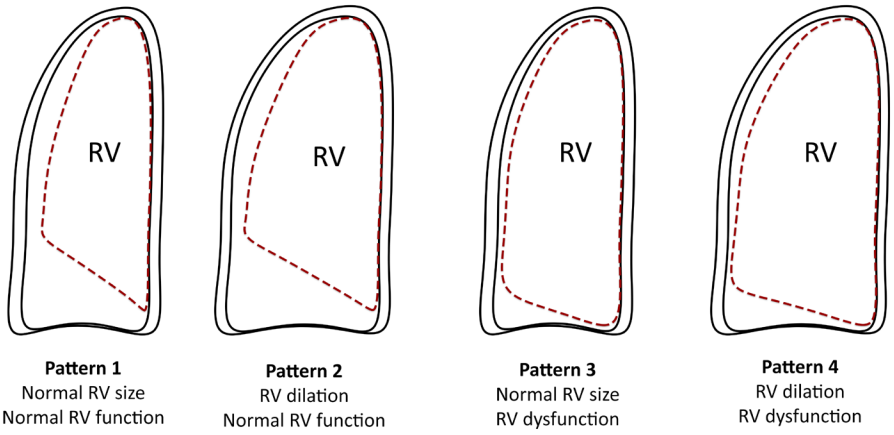


Figure 3. RV remodeling patterns as defined with the cut-off values derived from the spline curves of TA diameter and TAPSE vs. all-cause mortality

Four patterns of RV remodeling were defined according to the presence or absence of RV dilation and systolic dysfunction. RV dilation was defined as a tricuspid annulus diameter of ≥40 mm. RV systolic dysfunction was defined as a tricuspid annular plane systolic excursion of <17 mm.

RV = right ventricle; TA = tricuspid annulus, TAPSE = tricuspid annular plane systolic excursion

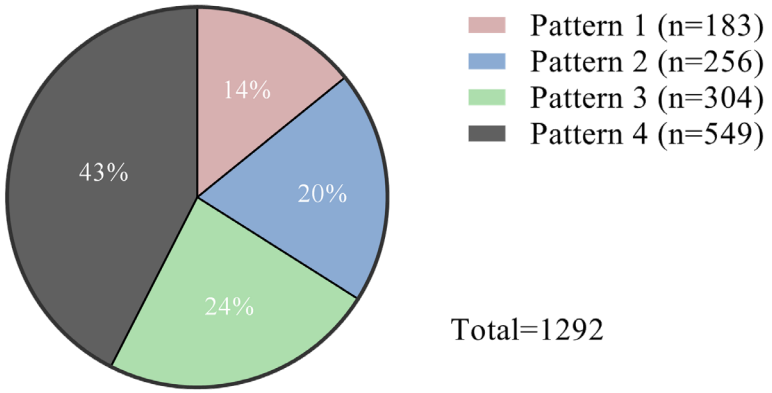


Figure 4. Distribution of right ventricular remodeling patterns in patients with significant secondary tricuspid regurgitation

Pattern 1 = normal RV size and systolic function; pattern 2 = dilated RV with normal systolic function; pattern 3 = normal RV size with RV systolic dysfunction; pattern 4 = dilated RV with systolic dysfunction.

RV = right ventricle

Table 1. Clinical characteristics of the total population and according to different patterns of RV remodeling

	Overall (n=1292)	Pattern 1 (n=183)	Pattern 2 (n=256)	Pattern 3 (n=304)	Pattern 4 (n=549)	P-value
Age (years)	71 (62-78)	71 (60-78)	70 (63-78)	72 (62-79)	71 (62-78	0.888
Male gender	642 (50)	57 (31)	134 (52)	110 (36)	341 (62)	**<0.001**
Body surface area (m^2)	1.9 ± 0.2	1.8 ± 0.2† §	2.0 ± 0.2* ‡	1.8 ± 0.2† §	1.9 ± 0.2* ‡	**<0.001**
Body mass index (kg/m^2)	26 ± 4	25 ± 4†	27 ± 5* ‡	25 ± 4† §	26 ± 4‡	**<0.001**
Medical history						
Dyspnea	601 (52)	68 (41)	114 (51)	146 (54)	273 (55)	**0.009**
Edema	240 (21)	31 (19)	36 (16)	52 (19)	121 (24)	0.058
Hypertension	964 (81)	134 (78)	185 (80)	221 (79)	424 (84)	0.242
Hypercholesterolemia	568 (48)	64 (37)	100 (44)	133 (48)	271 (54)	**0.001**
Diabetes mellitus	233 (20)	25 (15)	37 (16)	58 (21)	113 (22)	0.069
(Ex-)smoker	376 (32)	53 (31)	67 (29)	71 (25)	185 (37)	**0.011**
Coronary artery disease	484 (40)	46 (26)	68 (29)	124 (44)	246 (48)	**<0.001**
Pacemaker/ICD	464 (36)	48 (27)	105 (42)	93 (31)	218 (40)	**0.001**
Atrial fibrillation	590 (49)	59 (34)	115 (49)	125 (44)	291 (57)	**<0.001**
Chronic obstructive pulmonary disease	164 (14)	27 (16)	28 (12)	35 (12)	74 (15)	0.660
Laboratory values						
Hemoglobin (mmol/L)	7.9 (6.8-8.7)	8.0 (7.0-8.6) †	8.3 (7.4-9.1)* ‡ §	7.5 (6.3-8.5) †	7.8 (6.8-8.7) †	**<0.001**
Creatinine (µmol/L)	93 (74-123)	80 (67-106) † ‡ §	93 (74-115)* §	88 (72-125)* §	99 (81-136)* † ‡	**<0.001**
Urea (mmol/L)	8.5 (6.3-12.1)	7.3 (5.2-9.6) ‡ §	8.0 (6.2-11.4) §	8.5 (6.5-12.6)*	9.1 (6.6-13.5)* †	**<0.001**
Medication						
Diuretics	732 (62)	81 (48)	130 (57)	172 (63)	349 (69)	**<0.001**

*Values are mean ±SD, median (IQR) or n (%). P-value by Kruskal-Wallis or one-way ANOVA for non-Gaussian and Gaussian distributed continuous variables, respectively. P-value by chi-square test for categorical variables. (Bonferroni correction; *p < 0.05 vs. Pattern 1, †p < 0.05 vs. Pattern 2, ‡p < 0.05 vs. Pattern 3, § p < 0.05 vs. Pattern 4). ICD = implantable cardiac defibrillator; IQR = interquartile range; SD = standard deviation*

(49%) were known with permanent or paroxysmal atrial fibrillation.
In per-group analysis, patients with RV remodeling pattern 4 were more frequently male and presented more frequently with dyspnea and peripheral edema compared to the other RV remodeling patterns. This could be associated with the higher prevalence of comorbidities in this group. Hypercholesterolemia, smoking habit, pacemaker leads and atrial fibrillation were likewise more prevalent in RV remodeling pattern 4 compared to the other groups. In addition, patients with RV remodeling pattern 4 had worse renal function and used diuretics more frequently. There was a significant difference between the groups in terms of hemoglobin levels, with patients in RV remodeling pattern 2 having the highest value.

Echocardiographic variables

Table 2 summarizes the echocardiographic characteristics of the patients. The mean heart rate during echocardiographic assessment was 79±19 bpm, with 369 patients (30%) having atrial fibrillation. Four hundred ninety patients (38%) had a reduced (<40%) LVEF and about a quarter had concomitant significant aortic stenosis or mitral regurgitation (25% and 29%, respectively).

In per-group analysis, mid-range and reduced LVEF was more frequently observed among patients with more advanced patterns of RV remodeling (Figure 5). As expected, RV dimensions were larger in the RV remodeling patterns comprising RV dilation (pattern 2 and 4) compared to patterns 1 and 3. Likewise, LV dimensions were larger and the

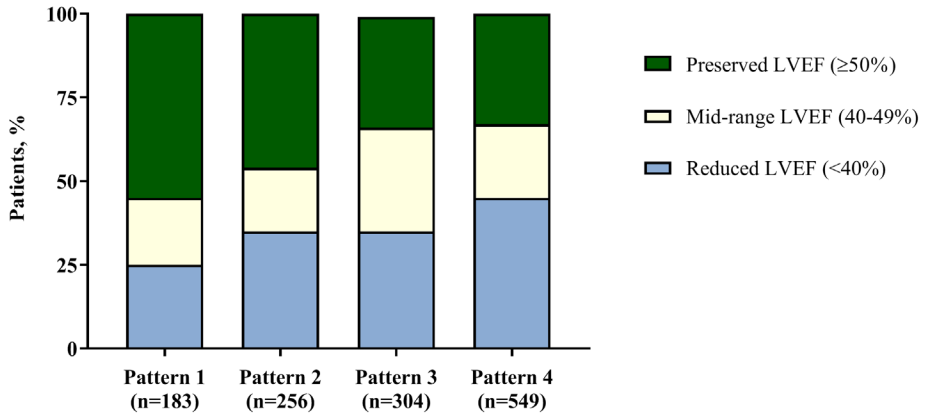


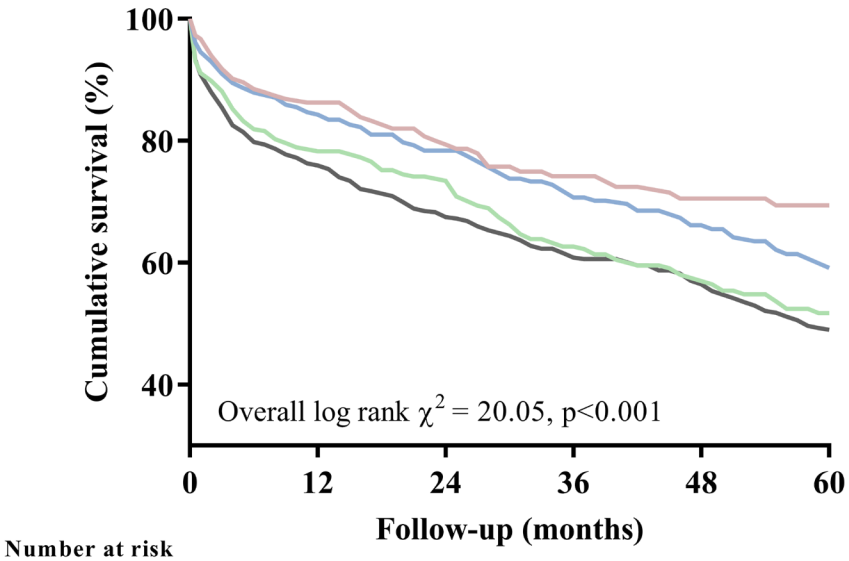
Figure 5. Association between left ventricular ejection fraction and patterns of right ventricular remodeling
LVEF = left ventricular ejection fraction

prevalence of moderate or severe mitral regurgitation was higher in RV remodeling patterns 2 and 4 compared to patterns 1 and 3. No significant differences were observed in RV systolic pressures across the different patterns of RV remodeling.

Prognostic impact of RV remodeling patterns

During a median follow-up of 34 months (IQR 0-60 months), 510 (40%) patients died. The cumulative 1- and 5-year survival rates were 80% and 55%, respectively. During follow- up, only 98 (8%) patients received tricuspid valve annuloplasty.

The Kaplan-Meier analysis showed significantly lower survival rates in patients with more advanced patterns of RV remodeling (log-rank chi-square 20.05; p<0.001; Figure 6). Interestingly, patterns 3 and 4 RV remodeling were associated with significantly



Number at risk

Pattern 1	183	154	119	91	71	59
Pattern 2	256	211	179	137	107	78
Pattern 3	304	239	203	153	109	77
Pattern 4	549	415	329	253	200	156

Figure 6. Kaplan-Meier curves for survival according to four patterns of right ventricular remodeling in patients with significant secondary tricuspid regurgitation

The Kaplan-Meier curves show significantly lower 5-year survival rates for patients with pattern 3 and 4 RV remodeling compared to both pattern 1 (52% and 49% vs. 70%; p=0.002 and p<0.001; respectively) and pattern 2 (52% and 49% vs. 60%; p=0.050 and p=0.004; respectively). RV = right ventricle

Table 2. Echocardiographic characteristics of the total population and according to different patterns of RV remodeling

	Overall (n=1292)	Pattern 1 (n=183)	Pattern 2 (n=256)	Pattern 3 (n=304)	Pattern 4 (n=549)	P-value
Heart rate (bpm)	79 ± 19	78 ± 17	76 ± 18‡ §	81 ± 20†	80 ± 19†	**0.003**
LV, LA and left-sided valvular disease						
LV diastolic diameter (mm/m²)	26 ± 6	26 ± 6	25 ± 6 §	26 ± 6	27 ± 6 †	**0.004**
LV systolic diameter (mm/m²)	21 ± 7	20 ± 7 §	20 ± 7 §	21 ± 7 §	22 ± 7 * † ‡	**<0.001**
LV end diastolic volume (ml/m²)	62 (45-93)	55 (41-78) §	61 (44-92)	56 (41-82) §	72 (51-105) * ‡	**<0.001**
LV end systolic volume (ml/m²)	34 (22-61)	27 (18-44) §	31 (20-58) §	30 (21-19) §	39 (25-73) * † ‡	**<0.001**
LVEF						**<0.001**
Preserved (≥50%)	497 (39)	100 (55)	116 (46)	103 (33)	178 (33)	
Mid-range (40-49%)	298 (23)	37 (20)	49 (19)	92 (31)	120 (22)	
Reduced (<40%)	490 (38)	45 (25)	90 (35)	107 (35)	248 (45)	
E/A ratio	1.6 (1.0-2.7)	1.1 (0.8-1.8) † ‡ §	1.6 (1.1-2.7) *	1.4 (1.0-2.6) *	2.0 (1.8-3.0) *	**<0.001**
LA maximum volume (ml/m²)	51 (34-70)	38 (26-55) † §	52 (36-69) * §	47 (27-65) §	58 (41-78) * † ‡	**<0.001**
Moderate and severe AS	290 (25)	36 (22)	46 (20)	78 (29)	130 (27)	0.057
Moderate and severe MR	369 (29)	44 (24)	76 (30)	72 (24)	177 (33)	**0.029**
RV and RA						
RV basal dimension (mm/m²)	24 ± 5	22 ± 4 † §	26 ± 4 * ‡	21 ± 3 † §	26 ± 4 * ‡	**<0.001**
RV mid dimension (mm/m²)	19 ± 5	17 ± 4 † §	20 ± 5 * ‡	17 ± 5 † §	20 ± 5 * ‡	**<0.001**
RV longitudinal diameter (mm/m²)	38 ± 6	37 ± 6 §	38 ± 6	37 ± 6 §	39 ± 6 * ‡	**0.001**
RV end diastolic area (mm²/m²)	13 (10-16)	11 (9-13) † §	13 (11-16) * ‡ §	11 (9-14) † §	14 (11-17) * † ‡	**<0.001**
RV end systolic area (mm²/ m²)	8 (6-11)	6 (5-8) † §	8 (6-10) * ‡ §	7 (5-9) † §	10 (7-12) * † ‡	**<0.001**
RV systolic pressure (mmHg)	36 ± 15	35 ± 13	36 ± 15	36 ± 16	36 ± 16	0.768
RA maximum area (mm²/m²)	15 ± 6	12 ± 4 † §	16 ± 6 * ‡	12 ± 4 † §	17 ± 6 * ‡	**<0.001**
RA long dimension (mm/m²)	33 ± 10	30 ± 6 † §	33 ± 6 *	31 ± 6 §	35 ± 13 * ‡	**<0.001**

RA short dimension (mm/m^2)	28 ± 6	25 ± 6 † §	28 ± 6 * ‡	26 ± 6 † §	30 ± 6 * ‡	**<0.001**
TAPSE (mm)	15 ± 5	21 ± 4 ‡ §	21 ± 4 ‡ §	12 ± 3 * †	12 ± 3 * †	**<0.001**
Tricuspid valve						
Moderate TR	1020 (79)	143 (78)	214 (84)	241 (79)	422 (77)	0.183
Severe TR	272 (21)	40 (22)	42 (16)	63 (21)	127 (23)	0.183
Valvular annulus diameter (mm)	42 ± 8	34 ± 4 † §	48 ± 7 * ‡	35 ± 4 † §	47 ± 6 * ‡	**<0.001**
Leaflet tenting height (mm)	10 (0-14)	4 (0-9) † ‡ §	11 (0-16) * ‡	8 (0-12) * † §	12 (6-16) * ‡	**<0.001**
Leaflet tenting area (mm^2)	2.5 (0-4.3)	0.6 (0-2.0) † ‡ §	3.1 (0-5.0) * ‡	1.7 (0-3.2) * † §	3.4 (1.4-4.9) * ‡	**<0.001**
PISA radius (mm)	11 (9-14)	9 (7-11) † ‡ §	12 (10-15) * ‡	11 (8-13) * † §	12 (10-15) * ‡	**<0.001**
EROA (mm^2)	69 (45-106)	46 (29-69) † ‡ §	79 (48-113) * ‡	62 (40-87) * † §	79 (52-122) * ‡	**<0.001**
RVol (ml/beat)	67 (42-104)	45 (22-72) † ‡ §	81 (46-124) * ‡	55 (37-86) * † §	78 (50-116) * ‡	**<0.001**
Regurgitant jet eccentricity	724 (57)	90 (51)	141 (56)	162 (54)	331 (61)	0.063

*Values are mean ±SD, median (IQR) or n (%). P-value by Kruskal-Wallis or one-way ANOVA for non-Gaussian and Gaussian distributed continuous variables, respectively. P-value by chi-square test for categorical variables. (Bonferroni correction; *p < 0.05 vs. Pattern 1, †p < 0.05 vs. Pattern 2, ‡p < 0.05 vs. Pattern 3, § p < 0.05 vs. Pattern 4). AF = atrial fibrillation; AS = aortic stenosis; E/A = ratio of mitral inflow peak early diastolic flow-velocity to atrial contraction peak-velocity; EROA = effective regurgitant orifice area; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PISA = proximal isovelocity surface area; RA = right atrium; RV = right ventricle; RVol = regurgitant volume; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation*

lower 5-year survival rates compared to both pattern 1 (52% and 49% vs. 70%; p=0.002 and p<0.001; respectively) and pattern 2 (52% and 49% vs. 60%; p=0.050 and p=0.004; respectively). When considering the presence of RV dysfunction only (defined as TAPSE<17mm), patients with RV dysfunction had significantly worse survival compared to patients with normal RV function (log-rank chi-square 17.95; p<0.001) (Supplemental Figure 1).

Univariable Cox regression analysis showed that older age, male sex, lower BSA and body mass index (BMI), symptoms of dyspnea, known coronary artery disease, pacemaker or implantable cardioverter defibrillator (ICD), LVEF, RV systolic pressure, hemoglobin, creatinine and urea levels, the use of diuretics and RV remodeling patterns were associated with all-cause mortality. Even though atrial fibrillation was more prevalent in pattern 4 RV remodeling, univariable analysis did not show an association with all-cause mortality (HR, 0.964; 95% CI, 0.806-1.152). At multivariable Cox regression analysis, patterns 3 and 4 of RV remodeling were independently associated with 48% and 41% increased risk of all-cause mortality, respectively (HR, 1.481; 95% CI, 1.056-2.075 and HR, 1.410; 95% CI, 1.023-1.943; respectively) (Table 3). When introducing TA diameter and TAPSE as continuous variables in the multivariable Cox regression analysis, TAPSE remained independently associated with all-cause mortality, while TA diameter was not (Supplemental Table 1). No independent association was observed between RV fractional area change and all-cause mortality (Supplemental Table 2).

DISCUSSION

In this large cohort of patients with moderate and severe secondary TR, RV remodeling varies significantly: RV dilation and systolic dysfunction was present in 43% of patients whereas 14% showed no dilation or systolic dysfunction of the RV. In addition, patients showing RV systolic dysfunction showed the lowest survival regardless of the RV dimensions.

RV remodeling patterns in TR

Secondary TR is characterized by dilation of the tricuspid valve annulus and tethering of the leaflets predominantly due to RV dilation and dysfunction. However, the RV remodeling process associated with secondary TR varies tremendously between patients. As shown in the present study, significant secondary TR may be present in patients with normal RV dimensions and function as well as in patients with RV dilation and/or dysfunction. The different patterns of RV remodeling may be related to the underlying

Table 3. Univariable and multivariable Cox proportional hazard models for all-cause mortality for patients with significant tricuspid regurgitation

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.019 (1.012-1.027)	**<0.001**	1.021 (1.013-1.029)	**<0.001**
Male gender	1.265 (1.063-1.505)	**0.008**	1.100 (0.910-1.331)	0.326
BSA (m^2)	0.517 (0.322-0.832)	**0.007**		
BMI (kg/m^2)	0.962 (0.938-0.988)	**0.004**		
Dyspnea	1.461 (1.222-1.746)	**<0.001**		
Hypercholesterolemia	1.029 (0.860-1.232)	0.752		
(Ex-)smoker	1.130 (0.935-1.367)	0.207		
Coronary artery disease	1.592 (1.338-1.894)	**<0.001**		
Pacemaker/ICD	1.302 (1.091-1.555)	**0.004**		
Atrial fibrillation	0.964 (0.806-1.152)	0.687		
LVEF		**<0.001**		**0.001**
Preserved vs. mid-range	1.160 (0.912-1.476)	0.226	1.058 (0.823-1.358)	0.661
Preserved vs. reduced	1.608 (1.315-1.965)	**<0.001**	1.440 (1.168-1.776)	**0.001**
RV systolic pressure (mmHg)	1.019 (1.014-1.025)	**<0.001**	1.016 (1.010-1.022)	**<0.001**
Severe TR	0.889 (0.721-1.906)	0.270		
Hemoglobin (mmol/L)	0.835 (0.776-0.898)	**<0.001**		
Creatinine (µmol/L)	1.004 (1.003-1.005)	**<0.001**	1.004 (1.003-1.004)	**<0.001**
Urea (mmol/L)	1.013 (1.010-1.017)	**<0.001**		
Diuretics	1.823 (1.488-2.234)	**<0.001**		
Remodeling Patterns		**<0.001**		**0.022**
Pattern 1 vs. pattern 2	1.169 (0.853-1.601)	0.175	1.057 (0.734-1.521)	0.766
Pattern 1 vs. pattern 3	1.514 (1.126-2.035)	**0.002**	1.476 (1.052-2.071)	**0.024**
Pattern 1 vs. pattern 4	1.560 (1.184-2.055)	**<0.001**	1.397 (1.013-1.927)	**0.042**

BMI = body mass index; BSA = body surface area; CI = confidence interval; ICD = implantable cardiac defibrillator; LVEF = left ventricular ejection fraction; RV = right ventricle; TR = tricuspid regurgitation

pathophysiology and to the timing in natural history of secondary TR when these patterns are assessed.

In patients without left-sided heart disease and without pulmonary hypertension, significant secondary TR may appear due to right atrial dilation and atrial fibrillation (so- called isolated TR) while the RV dimensions and function are within the normal values. Mutlak et al. (13) evaluated 242 patients with severe TR and identified 23 patients (9.5%) with secondary TR without significant pulmonary hypertension or left-sided heart

disease. Tricuspid annular dilation and atrial fibrillation were characteristic findings and right ventricular enlargement was present in approximately half of these patients (47%). In a study by Topilsky et al. (14) idiopathic TR was associated with basal RV enlargement (conical deformation) and tricuspid annulus dilation whereas pulmonary hypertension-related TR was associated with increased RV length (elliptical deformation), causing tenting of the tricuspid leaflets.

In patients with left-sided heart disease and pulmonary hypertension, secondary TR is associated with various grades of RV dilation and dysfunction. This group of patients is larger and more heterogeneous than the group of patients with pattern 1 RV remodeling (14). Left-sided heart disease, including severe LV systolic dysfunction, severe mitral regurgitation and aortic stenosis were frequent among patients with more advanced RV remodeling patterns in the present population. In the natural history of these diseases, progressive LV remodeling with hypertrophy, dilation and increased LV filling pressures that transmit to the left atrium and pulmonary circulation, leads to RV pressure overload. The thin-walled RV responds with myocardial hypertrophy and dilation to increase RV preload and to be able to rise mean pulmonary arterial pressure above 60 mmHg, maintaining RV systolic function (15). However, this remodeling process may lead to dilation of the tricuspid valve annulus and tethering of the tricuspid valve leaflets causing significant TR and volume overload that will further increase RV dimensions and wall tension. If left untreated, chronic increased afterload (pressure overload) and preload (volume overload) will impair RV coronary blood flow and contractility. In addition, myocyte loss and replacement and myocardial fibrosis may occur, reducing the possibility of RV functional recovery after correction of TR and impacting on survival. Therefore, characterization of RV remodeling in patients with significant TR is relevant to better determine the timing of tricuspid valve intervention.

Prognostic value of RV remodeling patterns in TR

The association of RV dilation and dysfunction with survival in patients with significant secondary TR in various groups of patients has been inconsistent. Kammerlander et al. (16) showed that RV systolic function, measured by fractional area change, was independently associated with survival in patients with secondary TR after left-sided valve surgery. In contrast, RV size and TR grade were not significantly associated with survival on multivariate analysis. In addition, Agricola et al. (17) demonstrated that in patients with heart failure with reduced left ventricular ejection fraction, the interaction between significant TR and TAPSE<16mm was independently associated with increased mortality whereas TR alone was not. Furthermore, among 519 patients with severe aortic stenosis

treated with transcatheter aortic valve replacement, those patients with RV dysfunction (TAPSE≤17mm) had worse survival irrespective of TR grade (18). In contrast, Lindman et al. (19) reported a significant association between significant TR and RV dilation with increased mortality in patients with severe aortic stenosis treated with transcatheter aortic valve replacement, whereas RV dysfunction had no prognostic value. Although many of the above-mentioned studies investigated the prognostic value of both RV dilation and RV dysfunction, none of those studies have considered the interaction of RV dilation and dysfunction and pattern of RV remodeling in their analysis. The present study provides incremental and novel evidence on the prognostic value of RV remodeling in a large cohort of patients with significant secondary TR. Patients with RV dysfunction, regardless of RV dimensions, had worse outcome compared to patients with preserved RV systolic function.

Interestingly atrial fibrillation was not associated with all-cause mortality in our study. The association between atrial fibrillation and outcome in patients with significant TR has not been extensively studied. While Nath and coworkers (20) did not investigate the association between atrial fibrillation and outcome in patients with TR, Topilksy et al. (21) demonstrated the association between severe isolated TR with all-cause mortality after correction for the presence of atrial fibrillation, but did not disclose whether AF itself was associated with all-cause mortality. In two studies analyzing outcome in patients with TR after left sided valve procedures, atrial fibrillation was not included in the multivariable Cox regression analysis (16, 22). Therefore, additional research is needed to elucidate the prognostic influence of atrial fibrillation in patients with significant TR.

Clinical implications

As shown in this study, the clinical presentation of patients with significant secondary TR varies tremendously. Since patterns of RV remodeling are closely related to etiology and prognosis in secondary TR, characterizing these patterns is important in daily clinical practice. The results of the current study support current guidelines in which tricuspid valve surgery should be considered in patients with symptomatic severe TR without severe RV systolic dysfunction. However, the best method and cut-off value to define severe RV systolic dysfunction remain to be established.

Study limitations

The limitations of this single-center study are inherent to its retrospective design. All-cause mortality was chosen as primary endpoint because the exact cause of death was not systematically recorded. A time span of 21 years was used for inclusion of patients in order to acquire the large cohort as presented. Assessment of RV systolic dysfunction by

2-dimensional echocardiography is challenging. In this study, TAPSE was used to define RV dysfunction as it is the most clinically available and validated method (7).

Conclusion

In a large cohort of patients with significant secondary TR, RV remodeling is a common finding at first diagnosis of moderate and severe TR and the pattern of RV remodeling is independently associated with all-cause mortality at long-term follow-up: patients with RV systolic dysfunction have worse clinical outcome regardless of the presence of RV dilation.

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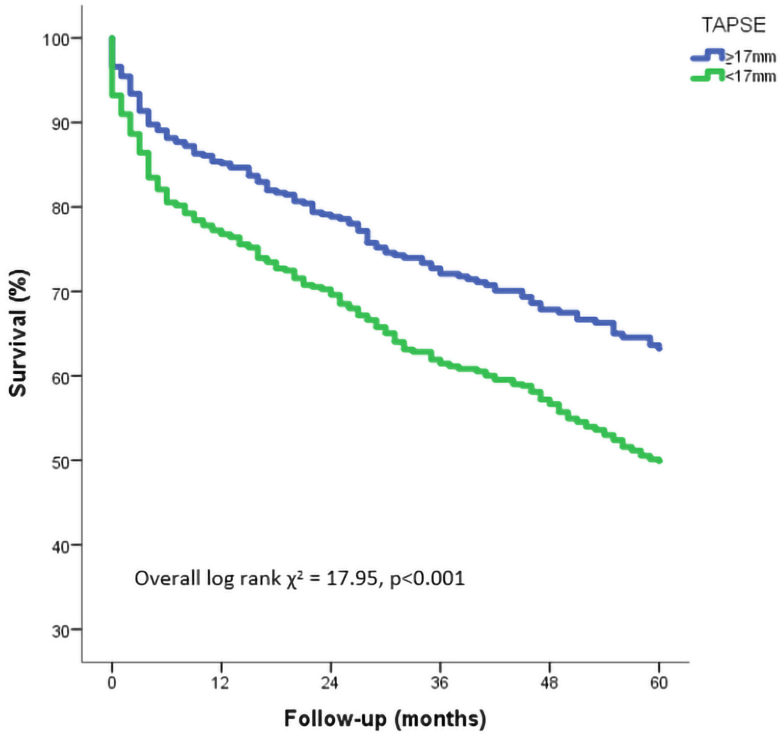
SUPPLEMENTAL MATERIAL



Number at risk

TAPSE ≥17mm	439	365	298	228	178	137
TAPSE <17mm	853	654	532	406	309	232

Supplemental Figure 1. Kaplan-Meier curves for survival according to TAPSE in patients with significant secondary tricuspid regurgitation

TAPSE = tricuspid annular plane systolic excursion

Supplemental table 1. Univariable and multivariable Cox regression analysis with tricuspid annulus diameter and TAPSE as continuous variables

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.019 (1.012-1.027)	**<0.001**	1.020 (1.012-1.028)	**<0.001**
Male gender	1.265 (1.063-1.505)	**0.008**	1.030 (0.849-1.249)	0.764
LVEF		**<0.001**		**0.005**
Preserved vs. midrange	1.160 (0.912-1.476)	0.226	1.043 (0.812-1.339)	0.741
Preserved vs. reduced	1.608 (1.315-1.965)	**<0.001**	1.377 (1.116-1.699)	**0.003**
Creatinine (µmol/L)	1.004 (1.003-1.005)	**<0.001**	1.003 (1.003-1.004)	**<0.001**
RV systolic pressure (mmHg)	1.019 (1.014-1.025)	**<0.001**	1.017 (1.011-1.023)	**<0.001**
Tricuspid annulus diameter (mm)	1.015 (1.004-1.026)	**0.006**	1.009 (0.997-1.022)	0.143
TAPSE (mm)	0.942 (0.924-0.961)	**<0.001**	0.953 (0.934-0.973)	**<0.001**

LVEF = left ventricular ejection fraction; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion

Supplemental table 2. Univariable and multivariable Cox regression analysis with tricuspid annulus diameter and RV fractional area change as continuous variables

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.019 (1.012-1.027)	**<0.001**	1.025 (1.016-1.035)	**<0.001**
Male gender	1.265 (1.063-1.505)	**0.008**	0.962 (0.773-1.196)	0.962
LVEF		**<0.001**		**0.006**
Preserved vs. midrange	1.160 (0.912-1.476)	0.226	1.021 (0.774-1.346)	0.884
Preserved vs. reduced	1.608 (1.315-1.965)	**<0.001**	1.417 (1.118-1.795)	**0.004**
Creatinine (µmol/L)	1.004 (1.003-1.005)	**<0.001**	1.004 (1.003-1.005)	**<0.001**
RV systolic pressure (mmHg)	1.019 (1.014-1.025)	**<0.001**	1.017 (1.011-1.024)	**<0.001**
Tricuspid annulus diameter (mm)	1.015 (1.004-1.026)	**0.006**	1.008 (0.994-1.023)	0.253
RV FAC (%)	0.984 (0.976-0.992)	**<0.001**	0.992 (0.983-1.000)	0.064

LVEF = left ventricular ejection fraction; RV = right ventricular; FAC = fractional area change